ANTIMICROBIAL STEWARDSHIP PROGRAMS: IMPLICATIONS FOR RESISTANCE RATES & QUALITY OF CARE IN HOSPITALS

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ABSTRACT

Alessandra Bassalobre Garcia Reeves: Antimicrobial Stewardship Programs: Implications for Resistance Rates & Quality of Care in Hospitals
(Under the direction Morris Weinberger)

Each year, two million Americans acquire serious infections caused by bacteria that are resistant to antibiotics resulting in significant morbidity, mortality, health care utilization and costs. Despite the recent passage of an antimicrobial stewardship programs (ASP) mandate in California and the Centers for Disease Control and Prevention (CDC) guidelines for a minimum standard ASP in hospitals, literature on the impact of ASPs on antimicrobial resistance (AMR) rates in hospitals is sparse.

The long-term goal of this study is to provide reliable evidence to influence policies and practices to reduce AMR and improve quality and clinical outcomes in hospitals. The overall objective of this study was to investigate the impact of ASP adoption, including the effect of a mandate in California and compliance with the CDC's 7 core elements on methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* (*C. diff*) in acute care hospitals. Then, we investigated their impact on selected quality and clinical outcomes.

In paper 1, we estimated the impact of passing an ASP mandate in California on hospital on MRSA and *C. diff* rates using 2013-2017 hospital-level data and a difference-in-difference with hospital fixed effects (FE) design. We found that, compared to hospitals in other states, California hospitals had significant ($p<0.05$) increases of 23%, 30%, and 20% in their MRSA SIR in 2015, 2016 and 2017, respectively. We also observed a 20% ($p<0.001$) decrease in their *C. diff* SIR in 2017.

Paper 2 examined the effect of statewide adoption of the CDC's ASP 7 core components on MRSA and *C. diff* rates using 2014-2016 data to estimate a state FE model. We found that the percentage of hospitals meeting the CDC's 7 core elements for ASP

between 2014 and 2016 increased in all states. A one percentage point increase in ASP compliance was associated with a 0.3% decrease ($p<0.01$) in *C. diff* infections in 2016 relative to 2014. We did not find an effect on MRSA infections.

In paper 3, we measured the association between rates of MRSA/*C. diff* and quality and clinical outcomes in US acute care hospitals using 2013-2017 hospital-level data and a hospital FE model. We found no association of MRSA or *C. diff* with 30-day readmissions, length of stay, 30-day mortality and intensive care unit days.

In summary, this study examined the various effects of an ASP state mandate and adoption of the CDC's 7 core elements, as well as the relationship between AMR and quality and clinical outcomes in hospitals. Our findings help fill important knowledge gaps and can assist policymakers and healthcare administrators make informed decisions on the regulation and implementation of ASPs. Future studies should seek data on hospital-level implementation of specific components of ASP and other resistant bacteria, neither of which is currently available.

My parents taught my brothers and I to work diligently, with excellence, but they never intended to have one of their children live in a different country, even to pursue a prestigious degree. I know it was not easy.

This dissertation is dedicated to them, for their personal sacrifice and unconditional love.
Clarice & Marco Aurélio

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LIST OF ABBREVIATIONS

AMR	antimicrobial resistance
ASPs	antimicrobial stewardship programs
C.diff	*Clostridioides difficile*
CAUTI	catheter-associated urinary tract infections
CDC	Centers for Disease Control and Prevention
CLABSI	central line-associated bloodstream infections
CMS	Centers for Medicare & Medicaid Services
DID	difference-in-difference
FE	fixed effects
HAIs	healthcare-associated infections
ICU	intensive care unit
IRB	Institutional Review Board
JC	Joint Commission
LoS	length of stay
MRSA	*Staphylococcus aureus*
NHSN	National Healthcare Safety Network
SB	Senate Bill
SD	standard deviation
SE	standard error
SHEA	Society for Healthcare Epidemiology of America
SIR	standardized infection ratio
SSI	select surgical site infections
US	United States
VA	Veterans Affairs
VRE	Vancomycin-resistant *Enterococcus*

CHAPTER 1. INTRODUCTION

Background

Each year, as many as 2 million Americans will acquire serious infections caused by bacteria that are resistant to one or more antibiotics resulting in 23,000 deaths, $20 billion in direct healthcare costs, and $35 billion in overall societal costs[1]. A major modifiable driver of antimicrobial resistance (AMR) is antibiotic prescribing and utilization practices[2]: up to 50% of antibiotic prescriptions are neither necessary nor appropriate in outpatient and inpatient settings[1,3].

Antimicrobial stewardship programs (ASPs) are universally recognized as essential tools in infection control throughout the healthcare system[4]. ASPs are associated with shorter hospitalizations and decreased antimicrobial consumption[5]. Studies on the effectiveness of ASPs are relatively recent and use varied assessment perspectives[6,7]. However, the impact of ASPs on actual AMR rates in hospitals is uncertain[5] or not explored.

My long-term goal is to provide reliable evidence to influence policies and practices to reduce the rates and associated consequences of AMR in hospitals. My overall study objective is to investigate the impact of an ASP mandate in California and distinguish standards of ASPs (CDC's 7 Core Elements) that may have a greater impact on reducing AMR rates in hospitals and, consequently, improving quality metrics nationwide. My central hypothesis is that hospitals with more restrictive ASPs (e.g., CA hospitals after the ASP mandate or those hospitals meeting the CDC's 7 Core Elements) will have lower AMR rates and higher quality care. This hypothesis is based on the meta-analysis by Karanika et al.[5], which found an overall reduction in AMR cases, general antimicrobial costs and length of hospitalization associated with the implementation of ASPs.

Specific Aims

I test my central hypothesis by pursuing the following specific aims:

Aim 1: Estimate the impact of passing an ASP mandate in California on hospital methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* (*C. diff*) rates. My hypothesis is that after July 2015, MRSA and *C. diff* rates dropped significantly in California compared to hospitals in other states. I use 2013-2017 HospitalCompare data and a difference-in-difference with hospital fixed effects (FE) design to estimate the effect of passing this bill.

Aim 2: Examine the association between statewide adoption of the CDC's 7 Core Elements of ASP and hospital MRSA and *C. diff* rates. My hypothesis is that states with a higher percentage of compliance to the CDC's 7 core elements for ASPs will have significantly lower MRSA and *C. diff* rates. States' percentage of adoption of the 7 core components over time (2014-2016) were retrieved from the CDC's Patient Safety Atlas dataset. I use 2014-2016 HospitalCompare data and fixed effects (FE) regressions to estimate this association.

Aim 3: Measure the association of MRSA and *C. diff* rates with quality and clinical outcomes in hospitals nationwide. My hypothesis is that higher rates of MRSA and *C. diff* in acute care hospitals are related to higher rates of 30-day hospital readmissions, 30-day mortality, longer length of hospital stay and more intensive care unit (ICU) days in US hospitals. To test these hypotheses, I use a hospital FE model and 2013-2017 HospitalCompare data.

This study will provide a nationwide overview of the effect of implementing ASP programs (statewide mandate, CDC core components) on AMR rates, as well as the relationship between AMR and quality and clinical outcomes in hospitals. Our findings can provide healthcare administrators and policy makers with evidence to support a mandate for minimum standard ASPs across the country. If effective, these strategies may help prevent the emergence of AMR, reduce the morbidity, mortality and health care costs associated with AMR infections in hospitals.

Significance

ASPs in hospitals shape prescribing practices and are intended to reduce the emergence of AMR. In hospital settings, ~40% of inpatients will receive antimicrobial agents as part of their treatment[8]; a large share of those prescriptions is neither necessary nor appropriate[1]. These sub-optimal practices are, at least in part, responsible for the emergence of AMR. Strategies to promote careful, discriminatory use of antimicrobial drugs can reduce AMR[9]. ASPs are universally recognized as essential tools in infection control throughout the healthcare system[4]. For example, formulary restrictions (or preauthorization), the most common type of ASP, can be especially impactful if enforced[5] because they directly address prescribing practices, preventing overuse and misuse of antimicrobials[10–12].

The assessment of ASPs is incipient and has not been standardized across studies in different states. Virginia and Kansas, for example, were assessed for their ASPs with different criteria[7,13], and a nationwide survey found that only 39% of acute care hospitals implemented CDC's 7 core elements of ASPs[6]. California is the only state that currently has an ASP mandate with specific requirements for hospitals. One study investigated how implementation of hospital ASPs changed after the passage of the mandate in California; however, it did not address its impact on hospital resistance rates[14].

Empirical evidence about the effects of different ASPs on AMR rates in hospitals is limited and not reliable. Although many studies examine ASPs in hospitals, most analyze their impact on prescribing practices and antibiotics use[11,12,15–17] rather than directly on AMR rates. The two US studies that included AMR rates as an outcome[18,19] have important methodological limitations. One did not address selection bias and the 1-year follow up period might have been too short to detect changes in the resistance rates[18]. In the other study, confounders and selection bias were not addressed at all[19]. One international study found lower AMR rates after implementation of ASP, although the study was susceptible to measurement error[20]. In this study, I will employ estimation methods that address ASP selection bias to examine actual AMR rates (MRSA and *C. diff*).

There is uncertainty around ASPs that are truly effective and the extent to which they affect AMR and quality metrics. A recent meta-analysis found that formulary restriction ASPs are associated with shorter hospitalizations and decreased general and restricted (broad spectrum) antimicrobial consumption and costs. However, results from the included studies were mixed[5], which is probably because the type and characteristics of ASPs were not addressed in detail. Whether or not ASPs meet the CDC's 7 core components were not addressed in those studies.

In summary, this research is significant because:

1) It will shed light on a major, persistent patient safety and healthcare quality problem within hospitals. Although preventable, AMR remains a prevalent, costly and deadly problem at the intersection of healthcare quality and safety. AMR also threatens global health security because of its potential to spread across patients, hospitals and countries[1,21]. This research seeks to unpack the effectiveness of an ASP mandate and the 7 core elements in preventing the emergence of AMR.

2) It addresses important gaps in the literature by providing a picture of how AMR may affect quality and clinical outcomes. A better evidence-based understanding of this relationship is important because it will help healthcare settings improve efficiency of their services and patient outcomes by preventing adverse events and the spread of resistant strain bacteria.

3) Understanding the impact of ASPs on AMR rates may have significant policy implications. The knowledge generated from this study can assist policymakers and healthcare administrators make informed decisions on implementing effective ASPs. Because most states do not have a mandate for ASPs, findings from this study could provide evidence for a minimum standard ASP to be required by state mandates in the future.

Innovation

AMR is a major public health problem lying at the intersection of healthcare quality and global health security that has not been successfully addressed[1,21]. AMR is not a novel problem, but it has gained more attention lately because of a rapid increase in resistance

rates, a small number of newly-developed antimicrobial agents[22], and its potential to spread across patients, hospitals and countries[21]. Most research to date has collected non-standardized information on ASP[6,7,13] and used prescribing practices, rather than AMR rates, as the outcome. One major challenge to previous research is that information on ASPs are not easily found in publicly available datasets.

This study is innovative because it represents a departure from the status quo by shifting focus to the effects of ASP as defined by the CDC on actual rates of AMR. We combined data from different sources to test hypotheses about the relationship between ASP and AMR using MRSA and *C. diff* infections as models. In our study, we combined state-level rates of compliance with the CDC standard for hospital ASPs with publicly available hospital-level MRSA and *C. diff* rates. This unique dataset allowed us to examine the association between CDC-standard ASPs and AMR rates. Because there are likely unmeasured hospital characteristics confounding this relationship, we will use a time and hospital fixed effects approach for more consistent estimates.

Moreover, we investigated the effect of California's mandate to adopt and implement a minimum-standard ASP in hospitals. Ours will be the first policy analysis that estimates the effect of such mandate in the real world. This study will not only generate new knowledge on the topic but also serve as a model for future research in the area. I will also examine the relationship between AMR rates and selected quality and clinical outcomes across hospitals nationwide, which offers greater external validity compared with previous studies that used single hospital settings.

CHAPTER 2. OVERALL METHODS

Conceptual Framework

The conceptual model for this study is adapted from Donabedian[23], which uses three categories of healthcare quality: structure (physical structure, financing model, equipment and staff), process (interactions and process through which care is delivered to patients) and outcomes (effects on quality metrics and health outcomes of patients)[23]. The ASP types, teams and characteristics (e.g., whether they meet CDC's 7 core components of ASP) are structural characteristics of a hospital that have the potential to directly shape antimicrobial prescribing (process) and, in turn, AMR rates through antimicrobial selective pressure (outcomes). AMR rates will affect other quality outcomes as a result (Figure 2.1). The box with confounders lists potential factors that could impact both ASP (main explanatory variable) and AMR rates (main outcome).

Antimicrobial selective pressure is the main driver of AMR. Any bacteria can develop resistance through continuous exposure to routinely used antibiotics. This continuous exposure is what defines selective pressure and causes bacterial genome to rapidly evolve through genomic mutations, resulting in resistant strains[24].

Approach

Aim 1: Estimate the impact of passing an ASP mandate in California on hospital MRSA and *C. diff* rates

Hypothesis: After July 1, 2015 (passage of California SB 1311), MRSA and *C. diff* rates dropped significantly in California compared to other states. We used a difference-in-difference with hospital FE model to estimate the effect of passing this bill.

Natural experiment: California's Senate Bill 1311, which was approved on September 29, 2014, required that, by July 1 2015, all acute care hospitals in the state to: (1) adopt and implement an ASP in accordance with federal and professional guidelines that includes the

monitoring and evaluation of the judicious use of antimicrobials; (2) form a physician-lead multidisciplinary antimicrobial stewardship committee; (3) appoint to that committee a physician or pharmacist who has expertise in antimicrobial stewardship through prior training or participation in continued education programs; and (4) report ASP activities to appropriate hospital committees leading quality improvement activities[25]. After the passage of the SB 1311, the percentage of hospitals in California which met CDC's 7 core elements for ASPs[26] increased 16.6%: from 59.3% in 2014 to 69.2% in 2015[14].

Data sources: We used 2013-2017 hospital-level data from the Centers for Medicare & Medicaid Services' (CMS) HospitalCompare, Provider of Service File and Medicare Cost Reports files. MRSA and *C. diff* are the only rates that are publicly available. While an ideal outcome measure would be the combined resistance rates of all relevant microorganisms, MRSA and *C. diff* are still reasonable proxies of resistance in hospitals.

Measures: The operational definition of each variable is presented, including the standardized infection ratio (SIR) for MRSA and *C. diff*[27], are presented in Table 2.1. SIRs account for differences between hospitals (e.g., hospital's patient case mix, hospital size, medical school affiliation). SIRs are defined as the ratio between number of infections detected by laboratorial tests and the number of infections predicted for a hospital with certain characteristics.

Research design: We used a difference-in-difference with hospital FE design to estimate the effect of the passage of an ASP mandate in California on MRSA and *C. diff* SIR. Since California was the only state in the US to pass a mandate with specific requirements, we included all the other states in the comparison group. We used time FE to control for time trends. The estimating equation is illustrated below. We used 2013 as the reference year.

Equation 1: $MRSA/C.diff\_SIR_{hst} = \beta_0 + \beta_1\, California_s + \beta_2 2014 + \beta_3 2015 + \beta_4 2016 + \beta_5 2017 + \beta_6 California_s * 2014 + \beta_7 California_s * 2015 + \beta_8 California_s * 2016 + \beta_9 California_s * 2017 + \beta_{10}\, X_{ht} + \varepsilon_{hst}$

Where X represents a vector of time-variant covariates, h is an index for hospital, s is an index for state and t is the time period. Variables are defined in Table 2.1.

Power calculations & sample size: From the few studies in the field, one found an 8 percentage point decrease in the rate of MRSA over the course of 4 years (52% vs 44%) after the implementation of a preauthorization policy[19]; another study found a 9.9 percentage point decrease in the rate of meropenem-resistant *P. aeruginosa* during the 6 years (13.7% vs 3.8%) after implementing a computerized preauthorization and a prospective audit policy[20]. For our power analysis, we used the proportions and effect size from the first case with a 95% significance level and 80% power. Based on these parameters, a sample size of 636 hospitals would be required in each group to detect an 8 percentage point difference.

Aim 2: Examine the association between statewide adoption of the CDC's 7 Core Elements of ASP and MRSA and *C. diff* rates in US states

Hypothesis: States with a higher percentage of compliance to the CDC's 7 core elements for ASPs will have significantly lower MRSA and *C. diff* rates. We tested this hypothesis by estimating a state and time FE model.

Justification & feasibility: The study of ASPs has not been consistently addressed or emphasized. However, the CDC has recently released guidelines for a minimum standard ASP, which includes 7 core components to support optimal antibiotic use: leadership commitment, accountability, drug expertise, action (implement at least one recommended action), tracking, reporting and education[26]. Moreover, previous studies have examined the impact of ASPs on antimicrobial usage[11,12,15–17] rather than AMR rates. Hospital adoption of ASPs is relevant because of the widespread use of antimicrobial agents in inpatient services[8], which makes them more susceptible to the emergence of resistant strains.

Data sources: Hospital-level measures of ASP are not publicly available. We merged different publicly available 2014-2016 data from HospitalCompare, Provider of Service and Medicare Cost Reports files. The state percentage of hospital adoption of the ASP 7 core components over time was retrieved from the CDC's Patient Safety Atlas website. The ASP

data from the Patient Safety Atlas website refers to acute care hospitals nationwide, collected through the CDC's National Healthcare Safety Network (NHSN).

Measures: The outcomes in this aim are the same as in aim 1. The main explanatory variable is ASP, which is defined as the percentage of hospitals that meet the CDC's 7 core components for ASPs[26] in a given state. Other time-variant control variables are listed in Table 2.1.

Research design: To account for time-invariant unmeasured confounders (Figure 2.1), we used a state and time FE estimation model. Our main regressor was the percentage of hospitals that meet the CDC's 7 core components for ASP in a given state over time (2014-2016). We estimated the association of this measure with two outcome variables: MRSA and *C. diff* SIR. We controlled for the time-variant characteristics listed in Table 2.1. We used Hausman tests to confirm model specification.

Equation 2: $MRSA/C.diff\_SIR_{st} = \beta_0 + \beta_1\, PctCompliance_{st} + \beta_2\, State_s + \beta_3\, Year_t + \beta_4\, X_{st} + \varepsilon_{st}$

Where X represents a vector of time-variant covariates, s is an index for state and t is the time period (variables are defined in Table 2.1).

Aim 3: Measure the association of MRSA and *C. diff* rates with quality and clinical outcomes in hospitals nationwide

Hypothesis: Higher rates of MRSA and *C. diff* in acute care hospitals are related to higher rates of 30-day hospital readmissions, 30-day mortality, longer length of stays, and more intensive care unit (ICU) days in US hospitals. We used hospital FE estimation methods to understand this association.

Justification & feasibility: This aim addresses the need to understand the impact of AMR on quality and clinical outcomes which may provide the basis for decisions by health services providers, administrators and policy makers to improve care. These outcomes have been studied separately in various studies[5,12,15,16,18–20]; however, results were mixed, selection bias was poorly addressed and some were not clearly described. Moreover, several studies used a single setting for the study. We analyze the relationship between

AMR rates and the selected outcomes across hospitals nationwide; therefore, results will be generalizable nationally.

Data sources: We used 2013-2017 data from HospitalCompare, Provider of Service and Medicare Cost Reports files. The outcome variables were 30-day readmissions, length of stay, 30-day mortality and ICU days. Key explanatory variables were MRSA and *C. diff* SIR. Variables are defined in Table 2.1. The sample represents acute care hospitals nationwide which provide health services to Medicare beneficiaries.

Research design: For each outcome, we estimated hospital and time FE models to control for time-invariant hospital characteristics that could confound the relationship between resistant strains and the outcomes of interest. We used clustered standard errors and weighted the regressions by hospital size. We used Hausman tests to confirm model specification.

Equation 3: $Quality/Clinical\_measures_{ht} = \beta_0 + \beta_1\, MRSA/C.diff\_SIR_{ht} + \beta_2\, Hosp_h + \beta_3\, Year_t + \beta_4\, X_{ht} + \varepsilon_{ht}$

Where X represents a vector of time-variant covariates, h is an index for hospital and t is the time period.

Power calculations & sample size: One study[28] observed an increased hazard of readmission (HR, 1.40; 95% CI, 1.33–1.46) for patients with a positive clinical culture for MRSA, Vancomycin-resistant *Enterococcus* (VRE) or *C. diff*. The 30-day readmission rate was 15% for patients with negative assay for those microorganisms and 25% for patients with a positive assay[28]. Therefore, we will use a 10% effect size, as well as 95% significance level and 80% statistical power for the power analysis. Based on these parameters, we will need at least 540 hospitals in total.

Sample

The flow chart in Figure 2.2 shows the hospital sample selected for the three aims. We included all CMS-certified hospitals in HospitalCompare from 2013-2017 and excluded VA hospitals (different data collection period), children's hospitals (different case mix/hospital epidemiology), and critical access hospitals. The latter are required to report infection data

only in some states and most do not have the minimum number of infections required to calculate SIR. We also excluded hospitals outside of the US (Figure 2.2).

Ethical Procedures

This proposal does not qualify as human subjects research as defined by federal regulations (45 CFR 46.102(f)). All datasets used in this research were publicly available. The datasets contain hospital names, which were de-identified, but no individual/personal information. Since this research does not involve interaction with any individual/hospital and hospital data were already publicly available, there is no risk of inadvertent disclosure. This study was submitted to the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill and did not require IRB approval since it does not constitute human subjects research (study # 18-3311).

Figures & Tables

Figure 2.1 Conceptual framework based on Donabedian[23]

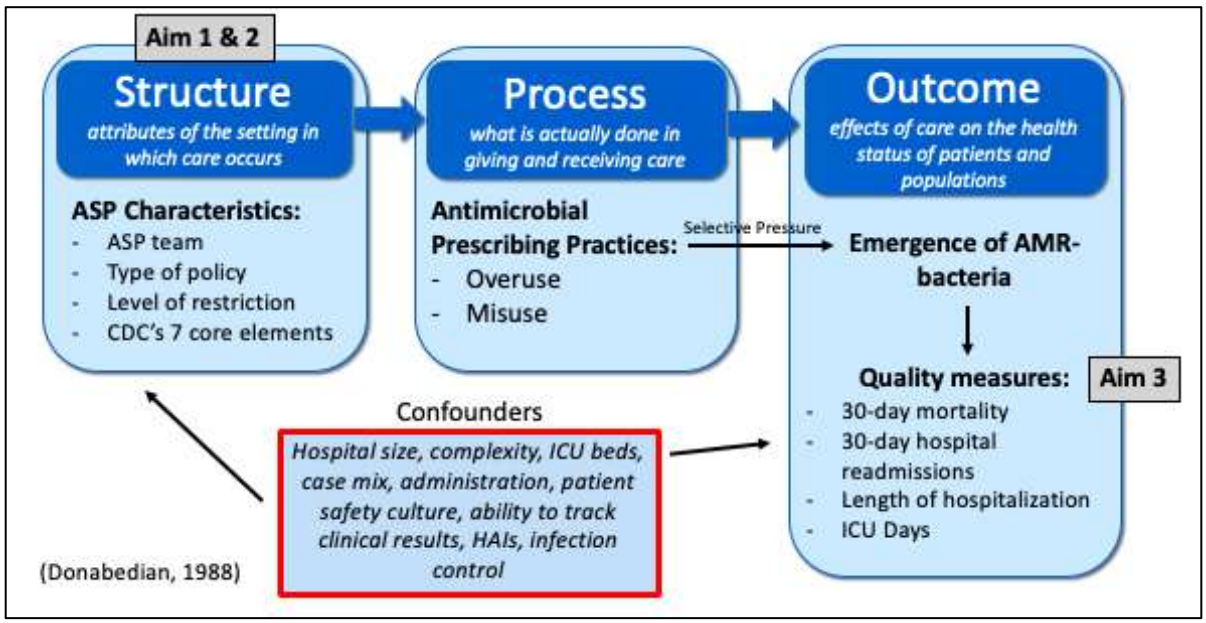


Figure 2.2 Inclusion and exclusion criteria for hospitals participating in the study

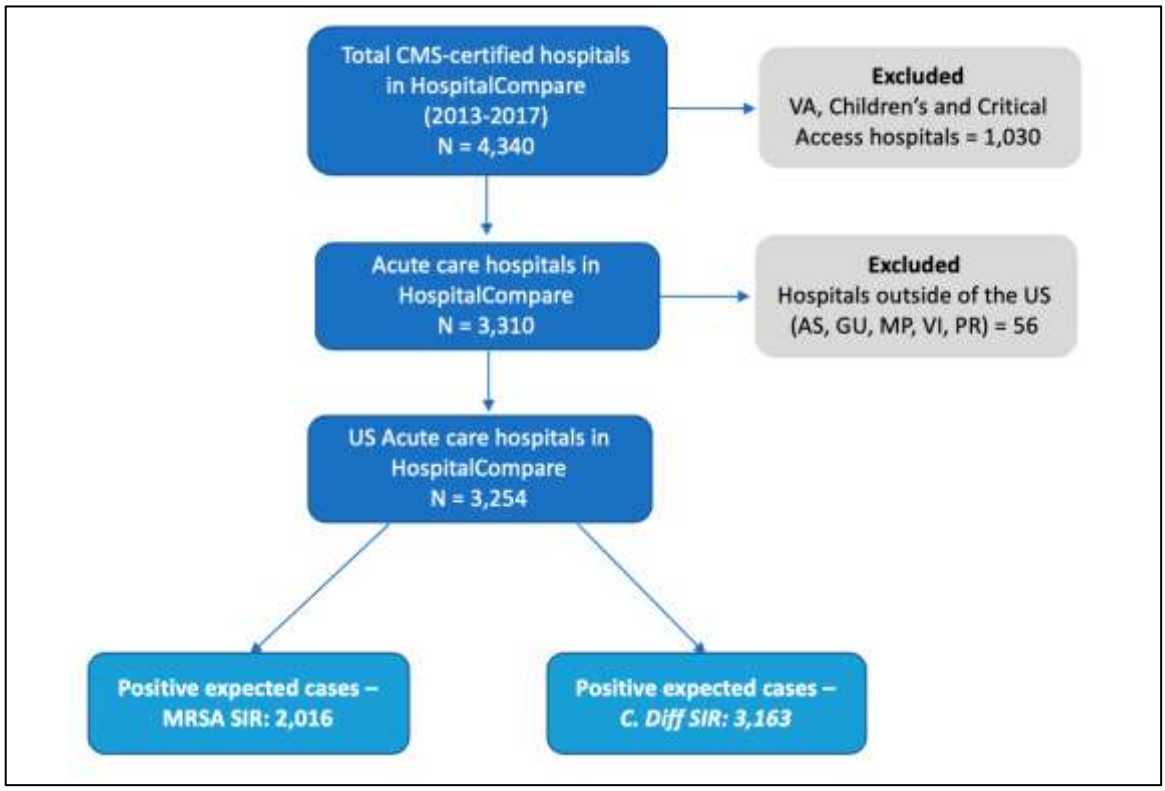


Table 2.1 Data source and variables description for aims 1-3, 2013-2017

Variable	Description	Source/Aim
Outcomes & Key Explanatory Variables		
MRSA[a] SIR[b]	MRSA standardized infection ratio: # observed MRSA bacteremia (laboratory-identified) divided by predicted # MRSA in the hospital. MRSA predicted events are calculated based on admission prevalence rate of MRSA infections, average length of stay, medical school affiliation, type of hospital, number of ICU beds, MRSA infections identified in the emergency department and/or observation units	HospitalCompare Outcome in aims 1 & 2, explanatory variable in aim 3
C. diff[c] SIR	*C. diff* standardized infection ratio: # observed *C. diff* (laboratory-identified) divided by predicted # *C. diff* in the hospital. *C. diff* predicted events are calculated using type of laboratory test used to identify *C. diff* infection, whether the hospital has emergency departments and/or observation units that collect stool specimens for *C. diff* testing, facility bed size, number of ICU beds, medical school affiliation, admission prevalence rate of *C. diff* infections, and type of hospital	Hospital Compare Outcome in aims 1 & 2, explanatory variable in aim 3
ASP[d] compliance	% of hospitals that meet the CDC's 7 core components for ASPs within a given state	CDC Patient Safety Atlas website Explanatory variable in aim 1
California	Dichotomous variable for whether the state is California (=1, 0 for other states)	Hospital Compare Explanatory variable in aim 2
30-day Readmission Rate	% patients re-admitted to the hospital within 30 days of discharge. Includes Medicare beneficiaries only and is adjusted for patient characteristics. Data collected annualy from July to June.	HospitalCompare Outcome in aim 3
30-day Mortality Rate	Death rate within 30 days of hospital admission for patients with selected diagnoses (weighted average of 30-day mortality for chronic obstructive pulmonary disease, heart attack, heart failure, pneumonia and stroke). Includes Medicare beneficiaries only and is adjusted for patient characteristics. Three-year moving average, from July to June (e.g.: 2017 mortality refers to data from July 2014 to June 2017).	HospitalCompare Outcome in aim 3
Length of stay	Mean length of inpatient stay in days	Medicare Cost Reports Outcome in aim 3
ICU[e] Days	Number of inpatient days spent in the ICU	Medicare Cost Reports Outcome in aim 3
Time-Invariant Variables (not included in the models)		
Hospital ownership	Categorical variable for public, private for-profit and private not-for-profit (referent category)	Hospital Compare
Rural	Dichotomous variable for whether the hospital is in a rural area (=1; 0 otherwise) according to their Core Based Statistical Area (CBSA) code	CMS[f] Provider of Service File
Emergency services	Dichotomous variable for whether the hospital provides emergency services (=1; 0 otherwise)	Hospital Compare

Variable	Description	Source/Aim
ICU Services	Dichotomous variable for whether the hospital provides intensive care services (=1; 0 otherwise)	CMS Provider of Service File
Time-Variant Control Variables		
Teaching hospital	Dichotomous variable for whether the hospital is affiliated with a medical school (=1; 0 otherwise)	CMS[d] Provider of Service File
Hospital size	Number of beds in the hospital	Medicare Cost Reports
Number of changes in ownership	Number of times hospital has undergone a change in ownership. Categorical variable for “No changes” (=1), “One time” (=2), “Two or more” (=3) changes in ownership within a given year	CMS Provider of Service File
% ICU beds	% of ICU beds relative to total beds in the hospital	Medicare Cost Reports
Quality accreditation	Dichotomous variable for whether the hospital is accredited by a CMS-approved accreditation organization (=1; 0 otherwise). Quality accreditation organizations include The Joint Commission (most of accredited hospitals), American Osteopathic Association Healthcare Facilities Accreditation Program, Det Norske Veritas Germanischer Lloyd, and Center for Improvement in Healthcare Quality	CMS Provider of Service File
Compliance with CMS requirements	Dichotomous variable for whether the hospital is in compliance with Medicare Conditions of Participation (CoP) for all services, areas and locations covered by the hospital's provider agreement under its CMS Certification Number (=1; 0 otherwise)	CMS Provider of Service File
Patient Safety Index	Composite measure of rates of pressure ulcer, iatrogenic pneumothorax, in-hospital fall with hip fracture, perioperative hemorrhage or hematoma, postoperative acute kidney injury, postoperative respiratory failure, perioperative pulmonary embolism (PE) or deep vein thrombosis (DVT), postoperative sepsis, postoperative wound dehiscence and unrecognized abdominopelvic accidental puncture/laceration. Includes Medicare beneficiaries only and is adjusted for patient characteristics. Two-year moving average, from July to June (e.g.: 2017 refers to data from July 2015 to June 2017).	Hospital Compare
Length of stay	Mean length of inpatient stay in days	Medicare Cost Reports
30-day Readmission Rate	% patients re-admitted to the hospital within 30 days of discharge. Includes Medicare beneficiaries only and is adjusted for patient characteristics. Data collected yearly from July to June.	Hospital Compare

[a] methicillin-resistant *Staphylococcus aureus*
[b] Standardized infection ratio
[c] *Clostridium difficile*
[d] Antimicrobial stewardship program
[e] Intensive Care Unit
[f] Centers for Medicare and Medicaid Services

CHAPTER 3. IMPACT OF CALIFORNIA'S MANDATE FOR ANTIMICROBIAL STEWARDSHIP PROGRAMS ON RATES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND *CLOSTRIDIOIDES DIFFICILE* IN ACUTE CARE HOSPITALS

Overview

Objective: Estimate the impact of California's Antimicrobial Stewardship Program (ASP) mandate on methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* (*C. diff*) rates in acute care hospitals. **Data Sources**: 2013-2017 data from the Centers for Medicare & Medicaid Services' (CMS) HospitalCompare, Provider of Service File and Medicare Cost Reports. **Study Design**: Difference-in-difference model with hospital fixed effects to compare CA with all other states before and after the ASP mandate. Outcomes: standardized infection ratio (SIR) for MRSA and *C. diff*. Time-variant covariates: medical school affiliation, bed count, quality accreditation, number of changes in ownership, compliance with CMS requirements, % intensive care unit beds, average length of stay, patient safety index, and 30-day readmissions rate. **Principal Findings**: In 2013, CA hospitals had an average MRSA SIR of 0.79 versus 0.94 in other states, and an average *C. diff* SIR of 1.01 versus 0.77 in other states. CA hospitals had increases ($p<0.05$) of 23%, 30%, and 20% in their MRSA SIR in 2015, 2016 and 2017, respectively. CA hospitals were associated with a 20% ($p<0.001$) decrease in their *C. diff* SIR only in 2017 compared to other states. **Conclusions**: The mandate was associated with a decrease in *C. diff* infections and an increase in MRSA SIR in California versus all other states.

Key words: antimicrobial resistance, antimicrobial stewardship programs, patient safety, methicillin-resistant *Staphylococcus aureus*, *Clostridioides difficile.*

Introduction

While antibiotics were considered life-savers in the 1940s, the widespread misuse of antimicrobials has diminished their effectiveness, representing a rapidly-growing threat to public health[29]. Each year, as many as 2 million Americans will acquire serious infections caused by bacteria resistant to one or more antibiotics resulting in 23,000 deaths, $20 billion in direct healthcare costs, and $35 billion in overall societal costs[1].

The problem is not confined to the United States. The World Health Organization considers antimicrobial resistance (AMR) an emerging global threat[30,31]. The United Nations General Assembly launched a global effort to tackle AMR in 2016, and the European Commission, World Health Organization, G-7 and G-20 countries recently launched an antimicrobial stewardship action plan to address this issue of "extraordinary gravity"[32,33].The problem has gained unprecedented political attention because antimicrobial consumption and the number of AMR infections are rapidly increasing in both developed and developing countries, where consumption increased 75% from 2000-2015[29,34].

Antibiotic prescribing and utilization practices are major modifiable drivers of AMR[2], with up to 50% of US antibiotic prescriptions being neither necessary nor appropriate in outpatient and inpatient settings[1,3]. AMR is a multifactorial issue that must be addressed on multiple fronts[35]. Some suggest a two-pronged approach: developing new antimicrobials to fight resistant strains while limiting use of current drugs to reduce rising resistance rates[36]. Our study will focus on the stewardship of current antimicrobials in hospitals.

Several organizations, including the Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA), have led national efforts to improve infection control and prescribing practices in healthcare settings[37]. One such approach is antimicrobial stewardship programs (ASP), a set of strategies designed to improve the appropriate use of antibiotics through optimal drug selection, dosage, duration of treatment, and administration. ASPs seek to provide effective treatment to patients while minimizing unintended consequences of antibiotic use[37].

In 2014, the CDC started recommending the adoption of ASPs by hospitals, and they have published a checklist to assist with implementing the seven core components of ASPs[38], which the CDC considers a minimum standard in hospitals. Those seven elements are related to the hospital's infrastructure and implementation of activities related to antimicrobial stewardship[26]. Veteran's Affairs (VA) Medical Centers have required ASPs since 2014. Moreover, through CDC's National Healthcare Safety Network (NHSN), acute care hospitals are currently required by the Centers for Medicare and Medicaid Services (CMS) to report five types of healthcare-associated infections (HAIs): central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), select surgical site infections (SSI), *Clostridioides difficile* (*C.diff*) infections, and methicillin-resistant *Staphylococcus aureus* (MRSA) infections[39].

Other initiatives also include the US Government's AMR Challenge, which started at the end of 2018[40], and the Antibiotic Use and Resistance module within NHSN reporting system[41]. The latter is currently optional, but some states have moved towards mandating its use[42]. Additionally, the CDC has recently increased funding for public health departments to work on and implement stewardship activities at the state and local levels[43].

While MRSA results from the development of resistant strains, *C. diff* is not technically a resistant bacteria; instead, *C. diff* is a bacteria with innate resistance to many antibiotics. It causes diarrheal disease after exposure to antibiotics which deplete the native microbiome and allow for its overpopulation. For that reason, *C. diff* infection is considered an antibiotic adverse event and indicator of antimicrobial use, which is also why it is used as an outcome in several studies addressing antimicrobial stewardship[44,45] and prescribing practices[46,47]. ASPs are universally recognized as essential tools in healthcare system infection control efforts[4]; In hospitals, ASPs are associated with shorter hospitalizations and decreased antimicrobial consumption[5].

At the state level, California has pioneered efforts to address AMR. In 2008, California started requiring hospitals to report rates of HAIs[48], and it has been the only state to mandate ASP in US hospitals since 2015[49]. In 2014, California's Senate Bill (SB) 1311,

required that, by July 1 2015, all California acute care hospitals: (1) adopt and implement an ASP in accordance with federal and professional guidelines (e.g., monitoring and evaluation of the judicious use of antimicrobials); (2) form a physician-led multidisciplinary antimicrobial stewardship committee; (3) appoint to that committee a physician or pharmacist with expertise in antimicrobial stewardship through prior training or continued education; and (4) report ASP activities to appropriate hospital committees leading quality improvement activities[25].

After the passage of the SB 1311, the percentage of hospitals in California which met CDC's 7 core elements for ASPs[26] increased from 59.3% in 2014 to 69.2% in 2015[14] and 81% in 2016[27]; however the effect of the CA law on AMR-related outcomes is still unknown. Although many studies examine ASPs at the hospital level, most analyze its impact on prescribing practices and antibiotics use[11,12,15–17] rather than directly on AMR rates. One of the major reasons for the lack of more assertive investigation is that information on ASPs and AMR rates are not generally available in publicly available datasets.

The present study estimates the impact of passing an ASP mandate in California (SB 1311) on MRSA and *C. diff* rates in acute care hospitals. Our hypothesis is that after 2015, MRSA and *C. diff* rates in acute care hospitals dropped significantly in California compared to other states. This study provides a novel approach to estimating the effect of such a mandate and can assist policymakers and healthcare administrators to make informed decisions on the implementation of ASPs.

Methods

Data sources

We merged 2013-2017 hospital-level data from the Centers for Medicare & Medicaid Services' (CMS) HospitalCompare, Provider of Service File and Medicare Cost Reports files. HospitalCompare compiles information about quality of care from over 4,000 Medicare-certified hospitals. Provider of Service Files contain data on hospital characteristics and type of services provided, and Medicare Cost Reports include utilization and cost data as well as facility characteristics for all Medicare-certified providers.

Subjects

We identified all CMS-certified acute care hospitals in the US for which MRSA/*C. diff* standardized infection ratio (SIR) data were available from 2013 through 2017. We excluded VA hospitals (different data collection period), children's hospitals (different case mix/hospital epidemiology), and critical access hospitals. The latter are required to report infection data only in some states, and most do not have the minimum number of infections required to calculate SIR.

Measures

We had two primary outcomes: MRSA SIR and *C. diff* SIR. The Hospital Compare system uses infection data from the CDC's NHSN, which calculates each hospital's MRSA SIR (ratio of MRSA bacteremia laboratory-identified events to the predicted number of MRSA bacteremia events) and *C. diff* SIR (ratio of *C. diff* laboratory-identified events to the predicted number of *C. diff* events).

MRSA predicted events are calculated by the NHSN based on admission prevalence rate of MRSA infections, average length of stay, medical school affiliation, type of hospital, number of ICU beds, and amount of MRSA infections identified in the emergency department and/or observation units. *C. diff* predicted events are calculated using the type of laboratory test used to identify *C. diff* infection, whether the hospital has emergency departments and/or observation units that collect stool specimens for *C. diff* testing, facility bed size, number of ICU beds, medical school affiliation, admission prevalence rate of *C. diff* infections, and type of hospital. The MRSA/*C. diff* SIR is calculated only for hospitals with at least one predicted event[39].

Our main explanatory variables are interactions between a dichotomous indicator of whether a hospital is located in California and the years after the mandate. Time-varying control variables included in the models were: medical school affiliation, bed count, quality accreditation, number of changes in ownership, compliance with CMS requirements, % intensive care unit beds, average length of stay, patient safety index, and 30-day readmissions rate. Operational definitions for each variable can be found in Table 3.1.

Analysis

We estimated a difference-in-difference (DID) model with hospital fixed effects (FE) for each outcome (MRSA SIR and *C. diff* SIR). We chose hospital FE because it controls for both unobserved as well as observed time-invariant hospital-specific characteristics, such as location (state, rural vs urban), hospital ownership, teaching status, specialty hospital, patient case mix, and structural factors, for example, infection control team, number/distance of sinks around hospital rooms, ability to track lab results electronically, safe surgery check lists, etc. Those characteristics are likely related to both our key variable of interest (being in California) and our outcomes (MRSA/*C. diff* SIR) and could confound the relationship estimated. Since several of these variables are not observed and mostly time-invariant, Hospital FE was chosen over other estimation methods.

We confirmed our model specification by using Hausman tests between a FE vs ordinary least squares model, and a FE vs random effects model. In both cases, coefficients in the FE model were significantly different from the other estimation methods, therefore, we selected the FE estimation to obtain consistent parameter estimates.

For the DID approach to provide unbiased estimates, two assumptions should hold. First, California is the only state being impacted by the policy change and there is no other shock happening at the same time; this assumption is reasonable as California was the only state to pass such legislation in the study period (2013-2017)[49]. Second, California and the other states should have parallel trends for MRSA and *C. diff* SIR in the pre-treatment period. This assumption was tested by the inclusion of an interaction between each year and our key explanatory variable. Robust standard errors were used to address heteroscedasticity among hospitals with varying sizes.

For sensitivity analyses, we estimated the models again including healthcare-associated infection (HAI) variables as controls since HAIs may be confounders in the estimated relationship. We also estimated the models again excluding states with <30% and <40% hospital adoption of the CDC's 7 core components for ASP from the control group. Since California had an initial high compliance with the 7 core elements, hospitals in states

with higher compliance could be a better counterfactual for hospitals California in this analysis.

Results

We included data for 2,016 and 3,163 acute care hospitals in the US in the MRSA and *C. diff* models respectively, which corresponds to 51.9% and 81.5% of the total acute care hospitals in the country. For MRSA, the SIR peaked in 2015 and then started decreasing in CA hospitals; other states had a less steep upward trend for MRSA in 2015 (Figure 3.1). For *C. diff*, trends were very similar between CA and other states before the mandate with a steeper decrease in CA after the mandate (Figure 3.2).

Table 3.1 provides descriptive statistics for California hospitals versus hospitals in other states before the mandate. In 2013, the average SIR in CA hospitals was 0.79 for MRSA (versus 0.94 in other states) and 1.01 for *C. diff* (versus 0.77 in other states). In terms of hospital characteristics, CA hospitals were larger, had a higher percentage of ICU beds and quality accredited hospitals, and a lower percentage of hospitals that were teaching, rural, had changed ownership, and were compliant with CMS requirements, compared to other states (Table 3.1). The sample size in both Tables 3.1 and 3.2 is larger for the *C. diff* model because there were more hospitals for which *C. diff* SIR was available, since that is a more common infection.

Table 3.2 provides adjusted estimates from the fixed effects regressions. Compared to hospitals in other states, CA hospitals had increases ($p<0.05$) of 23%, 30%, and 20% in their MRSA SIR in 2015, 2016 and 2017, respectively, although there was a downward trend after 2016 relative to other states. CA hospitals were associated with a 20% ($p<0.001$) decrease in their *C. diff* SIR only in 2017 (Table 3.2). Time trends were significant in 2015 and 2017 in the MRSA model and in 2015 and 2016 in the *C. diff* model. Quality accreditation was associated with an increased MRSA SIR.

In sensitivity analyses, results were robust to the inclusion of other healthcare-associated infection variables and the exclusion of states with <30% and <40% hospital adoption of the CDC's 7 core components for ASP.

Discussion

We analyzed whether California's SB 1311 supporting ASPs reduced MRSA and *C. diff* infections in acute care hospitals. Our results show that the CA mandate had significant associations with MRSA/*C. diff* SIRs; surprisingly, that association was in the opposite direction for MRSA.

C. diff SIR decreased after the mandate

Our findings support our hypothesis that the mandate in California would be associated with a reduction in the SIR for *C. diff*. The mandate introduced in SB 1311 was associated with a significant decrease in *C. diff* SIR in 2017, but a sharper downward trend can be observed in 2015 compared to other states (Figure 3.2). Other studies have also shown a decrease in *C. diff* rates after restricting antimicrobial use[50,51]. One study showed a 19% decrease in *C. diff* SIR after implementing antibiotic preauthorization combined with clinician education[52]. Another one detected a decrease as large as 66% in incidence of *C. diff* infections (incidence rate ratio = 0.34) after implementing revised antibiotic guidelines[50].

Moreover, it is estimated that hospital antibiotic prescribing could be improved in 37% of the cases, and a 30% reduction in broad-spectrum antibiotic use could result in a 26% decrease in *C. diff* infections[53]. In the outpatient setting a 10% reduction in antibiotic prescribing was associated with a 17% decrease in *C. diff* rates[47].

In a systematic literature review, ASP interventions in several different countries were associated with a decrease in *C. diff* incidence in 62.5% of the studies analyzed - especially in those implementing antimicrobial use restrictions, despite heterogeneity of interventions and ways in which outcomes were reported[44]. These findings are consistent with the fact that antibiotic use is the main driver for *C. diff*; therefore, *C. diff* rates should respond quicker to changes in ASPs compared to MRSA[54].

MRSA SIR increased after the mandate

One plausible explanation for the increase in the MRSA SIR in CA is that hospitals may have introduced processes and structures to proactively identify AMR cases (including MRSA), which peaked in 2015, and then started decreasing (Figure 3.1). Notably, California

had a lower MRSA SIR before the enactment of SB 1311, which may also contribute to our findings.

One possible reason for the increased MRSA is because the timeframe of this study coincided with the recent increased attention to the opioid epidemic, which has led to an increased incidence of MRSA bacteremia[55,56]. Furthermore, the impact of ASPs is likely stronger for gram-negative microorganisms since most of the restricted antibiotics are primarily for gram-negative bacteria, which is not the case of MRSA.

Another explanation is that resistant strains will likely not immediately respond to improved stewardship efforts, in part, because MRSA control is also dependent on improving infection prevention (i.e., increased hand hygiene, improved environmental disinfection, and reducing risk of CLABSI) and MRSA is very prevalent in the community (not only in healthcare settings). A 3-year ASP intervention, for example, has also been associated with increased MRSA incidence, although results should be interpreted with caution because of the small sample and single/international hospital setting[57]. However, a study that analyzed data from 6 post-intervention years found a large significant reduction in MRSA incidence in the last two years of the study[58].

MRSA and *C. diff* SIR increased in 2015

One explanation for the 2015 increase in both MRSA and *C. diff* SIR in CA and other states was the new baseline and improved method NHSN used to calculate predicted events starting in 2015. In prior years the baseline years used to calculate predicted infections were 2010-2011. According to the CDC, with the new baseline, MRSA/*C. diff* SIRs should shift closer to 1 nationwide[59], probably because of the models' improvement in predicting number of infections in each hospital. Since the re-baseline was implemented for all hospitals and, therefore, states nationwide and we also included time fixed effects in our analysis, this change should not be biasing our estimates and our results should still reflect the isolated effect of the mandate in CA.

Other ASP initiatives

California has been the only state to pass a mandate with specific ASP requirements as of 2017[49]; however, several factors may have increased ASP in hospitals in other states. One factor includes a voluntary adoption of hospital ASPs nationwide after the CDC launched the 7 core components for ASP[6,45] and the Joint Commission announced their new antimicrobial stewardship requirements that went into effect in 2017[60]. Both programs affect all CMS-certified hospitals nationwide, so our estimates should still be unbiased.

Regional and local initiatives may also increase ASPs. For example, Missouri Senate Bill 579, passed in 2016, requires strict reporting of HAIs and implementation of ASPs statewide by the end of 2017, although it does not provide specific ASP standards to be implemented[61]. Moreover, the largest healthcare system in Utah has been actively promoting ASP implementation in small community hospitals in the past few years[62]. Despite those scattered initiatives, we can still observe a significant impact of the CA mandate in acute care hospitals.

Limitations

We identified several limitations of our study. First, we could only assess 2 years of post-intervention data; to the extent that MRSA and *C. diff* rates would continue to fall, we would underestimate the impact of the legislation. Second, although CA hospitals' adoption of the CDC 7 core components for ASP increased from 58% in 2014 to 81% in 2016[27], we are not able to estimate the differential impact of specific antimicrobial policies or ASP components, only the overall impact of the mandate. Since ASP adoption did not reach 100% by 2017, that overall impact may have been attenuated by the few hospitals that did not adopt the minimum standard ASP proposed in the mandate. We are also not able to directly assess antimicrobial use as a mediating factor between ASP and AMR.

Third, since fixed effect models prioritize addressing bias over precision, we may have failed to detect smaller, statistically significant differences. There are also limitations for the external generalizability of the results, which can only be extrapolated for adult acute care hospitals not part of the VA system that have reported at least one MRSA/*C. diff* case

to the NHSN. Results may differ for other microorganisms; we restricted our study to MRSA and *C. diff* because data are publicly available through Hospital Compare. Finally, even though our data support the parallel trends assumption, we only have two years of pre-treatment data and are not able to verify time trends before that period.

Conclusion & Policy Implications

The CA mandate was associated with a decrease in *C. diff* rates in 2017. A sharper decrease in C. diff after 2015 is consistent with the fact that C. diff rates are driven largely by use of antibiotics. Contrary to our hypothesis, the CA ASP mandate was not associated with an immediate decrease in MRSA SIR. In response to the CA mandate, hospitals may have proactively identified AMR cases, which peaked in 2015, and then started decreasing as an expected lagged response to the mandate.

The effect of the mandate may have been diluted by the Joint Commission's 2016 nationwide ASP requirements, but we were still able to identify a significant impact in both outcome measures. More data on post-intervention years are needed to assess the long-term impact of the mandate.

This study has several policy implications. It is the first to shed light on a major and persistent healthcare problem by measuring the impact of a statewide ASP mandate. By doing so, it provides evidence on the effectiveness of antimicrobial stewardship at the hospital level for decision-makers at various levels of the healthcare system.

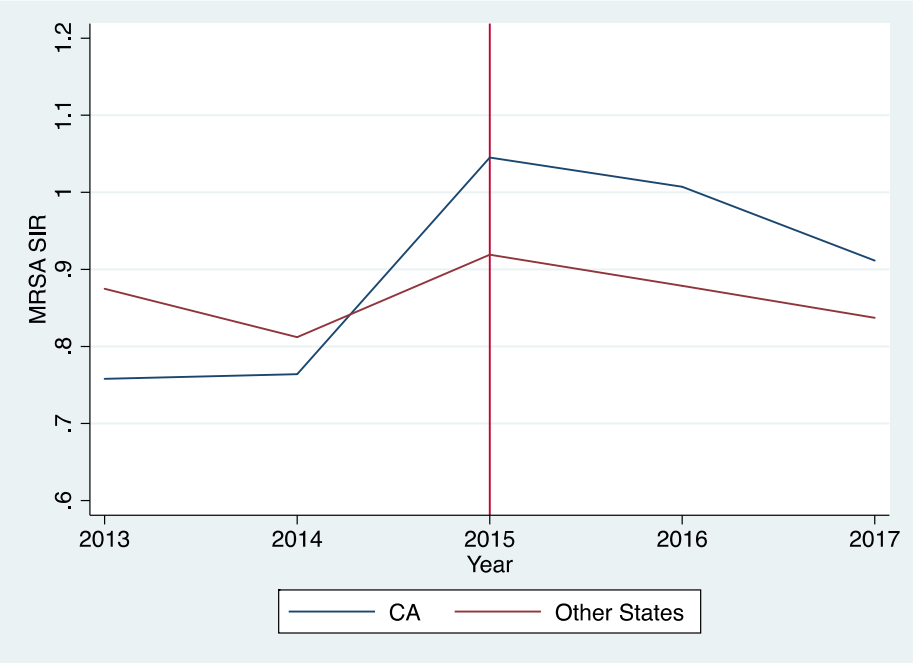
Evidence generated in this study can be used by healthcare administrators to understand the impact of antibiotic prescribing practices on patient and financial outcomes in their institution, to spur action towards adopting or improving their ASP according to federal guidelines, and to bring awareness of a possible under-identification of AMR cases. This study's results can also contribute to continued education of healthcare providers, improving their awareness of a broader picture of AMR and how compliance with stewardship actions can make an impact towards better healthcare.

Healthcare advocates and policy makers can use evidence from this study to assist hospitals to improve identification and reporting of AMR cases, as well as implement ASPs

at the regional/state level. Payers can use these results to create incentive mechanisms for the effective adoption of ASPs in terms of antibiotic use, timely identification of AMR cases, and decreasing rates of resistance. Since most states in the US do not have ASP legislation in place, this study can also serve as evidence for implementing regulation that requires a minimum standard ASP in acute care hospitals. Future research should evaluate the effect of other ASP mandates as additional states pass this type of regulation.

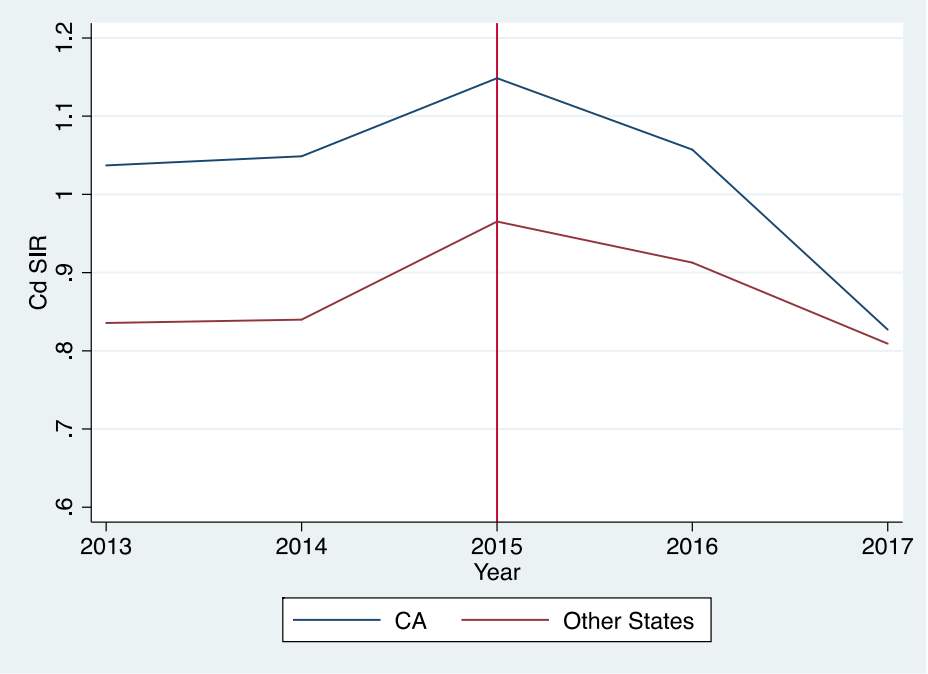
Figures & Tables

Figure 3.1 SIR[a] for MRSA[b] in California versus other states, 2013-2017



[a] Standardized infection ratio
[b] methicillin-resistant *Staphylococcus aureus*

Figure 3.2 SIR[a] for *C. diff*[b] in California versus other states, 2013-2017



[a] Standardized infection ratio
[b] *Clostridioides difficile*

Table 3.1 Descriptive statistics for MRSA[a] and *C. diff*[b] model by California versus other states in 2013

	MRSA Model			***C. diff* Model**		
Variable	**Other States (1,652)**	**CA (215)**	**p-value**	**Other States (2,754)**	**CA (281)**	**p-value**
MRSA SIR[c]	0.935	0.789	0.012			
C. diff SIR				0.765	1.012	0.000
Public	13.1%	16.7%	0.146	16.7%	17.8%	0.630
Private For Profit	17.7%	20.5%	0.328	20.7%	23.5%	0.280
Private Not For Profit	69.1%	62.8%	0.060	62.6%	58.7%	0.201
Teaching	47.2%	35.3%	0.001	33.9%	28.5%	0.067
Rural	11.7%	0.9%	0.000	29.5%	2.8%	0.000
Bed Count	358.4	312.6	0.009	251.2	265.2	0.335
Quality Accredited	97.2%	98.1%	0.430	90.8%	97.9%	0.000
Changes in ownership = 0	27.8%	47.0%	0.000	30.9%	47.3%	0.000
Changes in ownership = 1	32.6%	31.2%		31.1%	29.9%	
Changes in ownership >1	39.6%	21.9%		38.0%	22.8%	
Compliant CMS[d] requirements	76.3%	65.6%	0.001	77.7%	66.9%	0.000
Emergency Services	98.7%	97.7%	0.251	96.7%	94.7%	0.084
% ICU[e] beds	8.1%	9.6%	0.000	7.7%	9.2%	0.000
Length of Stay (days)	3.6	3.5	0.038	3.4	3.4	0.462
ICU Services	94.2%	96.7%	0.123	86.9%	95.4%	0.000
Patient Safety Index	0.875	0.887	0.475	0.858	0.879	0.096
% Hospital Readmissions	15.7%	15.6%	0.088	15.6%	15.5%	0.049

[a] methicillin-resistant *Staphylococcus aureus*
[b] *Clostridioides difficile*
[c] Standardized infection ratio
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit

Table 3.2 Regression-adjusted estimates for the effect of the ASP[a] mandate in California on MRSA[b] and *C. diff*[c] SIRs[d], 2013-2017

	MRSA MODEL	***C. DIFF* MODEL**
VARIABLE	**b(SE)**	**b(SE)**
2014	-0.027 (0.023)	0.01 (0.009)
2015	0.054* (0.026)	0.133*** (0.012)
2016	-0.003 (0.027)	0.062*** (0.013)
2017	-0.076** (0.027)	-0.024 (0.013)
CA **x** 2014	0.044 (0.063)	0.008 (0.028)
CA **x** 2015	0.233** (0.078)	0.005 (0.037)
CA **x** 2016	0.304*** (0.077)	-0.047 (0.036)
CA **x** 2017	0.198* (0.083)	-0.200*** (0.043)
TEACHING	-0.061 (0.067)	-0.02 (0.029)
BED COUNT	0.000 (0.000)	-0.000 (0.000)
QUALITY ACCREDITED	0.214* (0.093)	-0.025 (0.049)
CHANGES IN ONWERSHIP = 1	0.027 (0.177)	0.068 (0.07)
CHANGES IN ONWERSHIP >1	0.147 (0.235)	0.076 (0.093)
COMPLIANT CMS[E] REQUIREMENTS	0.033 (0.051)	0.004 (0.028)
% ICU[F] BEDS	-0.009 (0.005)	0.002 (0.003)
LENGTH OF STAY	0.034 (0.031)	0.016 (0.015)
PATIENT SAFETY INDEX	0.001 (0.057)	-0.003 (0.025)
HOSPITAL READMISSIONS	0.011 (0.018)	0.000 (0.007)
CONSTANT	0.377 (0.384)	0.731*** (0.153)
N	8,595	14,245
R^2	0.011	0.031

[a] Antimicrobial Stewardship Program
[b] methicillin-resistant *Staphylococcus aureus*
[c] *Clostridioides difficile*
[d] Standardized infection ratios
[e] Centers for Medicare and Medicaid Services
[f] Intensive Care Unit
* p<0.05
** p<0.01
*** p<0.001

CHAPTER 4. ASSOCIATION BETWEEN STATEWIDE ADOPTION OF THE CDC'S 7 CORE ELEMENTS OF ANTIMICROBIAL STEWARDSHIP PROGRAMS AND RATES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND *CLOSTRIDIOIDES DIFFICILE* IN US STATES

Overview

Objective: Measure the association between statewide adoption of the Centers for Disease Control and Prevention's (CDC) antimicrobial stewardship program (ASP) 7 core components and hospital methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile (C. diff)* rates in US states. Hypothesis: States with a higher percentage of compliance to CDC's 7 core components for ASPs will have significantly lower MRSA and *C. diff* rates. **Participants:** all US states. **Design:** Observational longitudinal study. **Methods:** Data: We used 2014-2016 data from HospitalCompare, Provider of Service File, Medicare Cost Reports, and the Patient Safety Atlas website. Outcomes: Methicillin-resistant *staphylococcus aureus* (MRSA) standardized infection ratio (SIR) and *Clostridioides difficile* SIR. Key explanatory variable: percentage of hospitals that meet the CDC's 7 core components for ASP in each state. Analysis: We estimated state and time fixed effects models with time-variant controls and weighted our analyses by number of hospitals in the state. **Results:** The percentage of hospitals meeting the CDC's 7 core components for ASP between 2014 and 2016 increased in all states. A one percentage point increase in %ASP compliance was associated with a 0.3% decrease ($p<0.01$) in *C. diff* infections in 2016 relative to 2014. We did not find an effect on MRSA infections. **Conclusions:** Comprehensive ASPs can positively impact *C. diff* SIR in acute care hospitals. We did not find evidence of an impact on MRSA SIR, probably due to the short length of the study and variety of stewardship strategies that ASPs may encompass.

Introduction

Antimicrobial resistance (AMR) is a major public health threat lying at the intersection of healthcare quality and global health security[1,21]. In the US in 2013, AMR resulted in 23,000 deaths, $20 billion in direct healthcare costs and $35 billion in overall societal costs[1].

Resistance to the first antimicrobial, penicillin, was reported in 1942, soon after its discovery[63]. AMR is not a novel problem, but it has recently gained great attention because of a rapid increase in resistance rates and the small number of new antimicrobial agents[22]. It takes several years for a new antibiotic to be developed and much shorter time for bacteria to become resistant to it.

Misuse and overuse of antimicrobials are major causes of AMR, such as methicillin-resistant *Staphylococcus aureus* (MRSA) infections. There is an important opportunity for reducing the incidence and impact of AMR because up to 50% of all antimicrobials prescribed in US acute care hospitals are unnecessary or inappropriate[64–67]. Beyond resistance, incorrect antibiotic prescribing can also lead to adverse events (sometimes severe) and ~250,000 *Clostridioides difficile* (*C. diff*) infections in hospitalized patients every year[1], with no therapeutic benefit[53,68,69]. *C. diff* is not technically a resistant bacteria but it has an innate resistance to many antibiotics and is vastly used as a marker for antimicrobial use because it thrives when the normal human microbiome is killed by the use of antimicrobials.

As a management tool for hospitals, antimicrobial stewardship programs (ASPs) can help ensure that antimicrobials are only prescribed when needed and that the right antimicrobial, dose and duration of treatment are being prescribed[26]. Although ASPs can take different approaches (e.g., antibiotic time outs, prior authorization, prospective audit and feedback), all involve stricter assessment and monitoring of antimicrobial use and sometimes restricting the use of broad spectrum agents[5,26].

A growing body of evidence has shown that ASPs can optimize antimicrobial use[18,70,71], reduce adverse events[18] and resistance rates[72], improving quality of care and patient safety. Reduced antimicrobial use has not been shown to negatively affect, and may improve, patient outcomes[73]. As noted, most ASP literature focuses on prescribing practices

or antimicrobial use[5,71,74] rather than resistance rates. Moreover, most studies that assessed the impact of ASP on infection rates were done in a single and/or international setting, so external generalizability is compromised[44].

Controlling the emergence and spread of resistant microorganisms is a national priority. The Centers for Disease Control and Prevention (CDC) has launched a series of initiatives and guidelines to address the problem. In 2006, the CDC published guidelines on managing multi-drug resistant organisms in healthcare settings[75]; in 2009, it launched the "Get Smart for Healthcare Campaign", to promote improved antibiotic use; and in 2013, it published a thorough report on the epidemiology and morbidity of resistant bacteria and *C. diff* [1], and listed the "loss of antibiotic protection" as one of the top public health concerns in the country[76].

Finally, in 2014, the CDC launched specific guidelines for ASPs in acute care hospitals as well as other healthcare settings[26]. Those guidelines add to the previous work of the Society for Healthcare Epidemiology of America, Infectious Disease Society of America, and The Joint Commission[26,77]. It sets a minimum standard, with 7 core elements for hospitals' ASPs: leadership commitment, accountability, drug expertise, action, tracking, reporting and education[26].

Despite these efforts, a national survey found that only 64% of hospitals in the country had some type of ASP policy in place in 2011. Larger, urban and teaching hospitals were more likely to have such policies; antibiograms and antimicrobial restriction policies were the most common[78]. Another nationwide survey conducted in 2014 found that 39% of acute care hospitals had implemented CDC's 7 core elements for ASPs. At the state level, uptake ranged from 7-58%[6]. In 2015, that increased to 48.1%, with the highest increase in the leadership commitment component[79]. Larger hospitals and leadership support were associated with a comprehensive ASP in 2014 and 2015[79,80], teaching status was also significantly associated with the presence of ASP in 2015[79].

Despite CDC's recent release of guidelines for a minimum standard ASP and its assessment in hospitals, the effect of implementing the 7 core elements on resistance rates

and *C. diff* infections is still unclear. Furthermore, the impact of ASPs on actual AMR rates in hospitals is uncertain or not explored.

The objective of this study was to examine compliance with CDC's ASP 7 core components between 2014 and 2016, as well as the association between statewide adoption of the CDC's ASP 7 core components and hospital MRSA and *C. diff* rates in all US states. We hypothesized that: (1) compliance with the CDC's ASP 7 core components would increase between 2014 and 2016; and (2) states with a higher percentage of compliance to CDC's 7 core components for ASPs will have significantly lower MRSA and *C. diff* rates.

Methods

Data sources

We merged 2014-2017 hospital-level data from the Centers for Medicare & Medicaid Services' (CMS) HospitalCompare, Provider of Service File, Medicare Cost Reports, and 2014-2016 state-level data from CDC's Patient Safety Atlas website. HospitalCompare compiles quality of care information from over 4,000 Medicare-certified hospitals, Provider of Service Files contain data on hospital characteristics and type of services provided, and Medicare Cost Reports includes utilization and cost data besides facility characteristics regarding all Medicare-certified providers. The CDC's Patient Safety Atlas website has state-level data on hospital-acquired infections, antimicrobial resistance and ASPs from acute care hospitals nationwide, collected through the CDC National Healthcare Safety Network's (NHSN) Patient Safety Component Annual Hospital Survey, which assesses compliance with the 7 core components of ASP.

Subjects

The study population includes all 50 US states plus DC from 2014-2016. The data that were originally at the hospital-level were collapsed at the state-level using hospital size weights. Hospital-level data included all Medicare-certified acute care hospitals in the US for which MRSA/*C. diff* standardized infection ratio (SIR) data were available from 2014-2016. Veteran Affairs (VA), children's and critical access hospitals were excluded because of

different data collection period, different case mix/hospital epidemiology and lack of reporting requirements for infection data, respectively.

Measures

Table 4.1 contains operational definitions for each variable. Our two outcomes are defined as follows: MRSA SIR is the ratio of MRSA bacteremia laboratory-identified events to the predicted number of MRSA bacteremia events; *C. diff* SIR is the ratio of *C. diff* laboratory-identified events to the predicted number of *C. diff* events. SIRs are calculated for each hospital by the CDC's NHSN and made available through HospitalCompare's data system.

MRSA and *C. diff* predicted events are calculated by the NHSN based on several predictors. For MRSA, they take into account admission prevalence rate of MRSA infections, average length of stay, medical school affiliation, type of hospital, number of ICU beds, and amount of MRSA infections identified in the emergency department and/or observation units. *C. diff* predicted events are calculated using type of laboratory test used to identify infection, whether the hospital has emergency departments and/or observation units that collect stool specimens for testing, facility bed size, number of ICU beds, medical school affiliation, admission prevalence rate of *C. diff* infections, and type of hospital. The MRSA and *C. diff* SIRs are calculated only for hospitals with at least one predicted event[39].

Our main regressor is the percentage of hospitals that meet the CDC's 7 core components for ASP in a given state over time (2014-2016). The CDC's Patient Safety Atlas website shows a substantial increase in the percentage of compliance in every state nationwide from 2014-2016[27]. Time-variant independent variables included in the models were: type of ownership, emergency services, intensive care unit (ICU) services, medical school affiliation, bed count, quality accreditation, number of changes in ownership, compliance with CMS requirements, %ICU beds, average length of stay, patient safety index, and 30-day readmissions rate.

Analysis

First, we used descriptive statistics to measure state-level variation in the percentage of hospitals meeting the CDC's 7 core components for ASP between 2014-2016. Then, for each outcome, we estimated a set of different models using state fixed effects (FE).

We chose state FE because there are a number of time-invariant unmeasured confounders to the relationship between ASP and resistance/*C. diff* rates. These include location (state, rural vs urban), hospital ownership, teaching status, specialty hospital, patient case mix and structural factors. Since some of these variables are unobserved, we are not able to verify whether they are truly time-invariant, but we assume they have very little variation, if any variation at all.

As we used state-level analyses due to the availability of ASP data only at the state level, hospital data were aggregated at the state level using hospital size weights. The analyses were weighted by number of hospitals in each state, and we controlled for the time-varying characteristics listed in Table 4.1. In terms of model specification, we ran a Hausman test to assess whether the FE model was preferred to a random effects model.

We also tested using a lagged explanatory variable (2014-2016 ASP data and 2015-2017 outcomes) to address a possible reverse causation, and an interaction between ASP and time (years) to test whether there could be differential treatment effects in each specific year. Moreover, we re-estimated the models using hospital-level data, even though there was ASP variation only at the state level (Appendices A.1-A.3).

Results

Increases in the percentage of hospitals meeting the CDC's 7 core components for ASP between 2014 and 2016 ranged from 6-62% points (Figure 4.1). States with a smaller absolute increase usually had a higher percentage in 2014. For example, states with ≥50% compliance in 2014, such as AZ, CA, ID, MA, ME, NY and UT, had only 6-26% point increases in ASP compliance by 2016. Similarly, states with only ≤29% compliance in 2014, such as CT, DC, HI, TN and WV, had the highest absolute increases in percentage of hospitals meeting the 7 core components (36-62% points).

We hypothesized that states with a higher percentage of compliance to CDC's 7 core components for ASPs would have significantly lower MRSA and *C. diff* rates. Our findings do not support our hypothesis for MRSA (Table 4.2). However, there was support for our hypothesis in the *C. diff* model where ASP compliance was interacted with year. A one percentage point increase in ASP compliance was associated with a 0.3% decrease ($p<0.01$) in *C. diff* infections in 2016 relative to 2014 (Table 4.3). This result suggests a differential treatment effect of increasing ASP compliance at the state level across years.

We did not find evidence of a lagged effect of %ASP compliance in any of the models. Results in the MRSA and *C. diff* models were consistent in both state-level and hospital-level analyses (Appendices A.1-A.3).

Discussion

AMR is a major public health threat resulting in extensive morbidity, mortality, and health care costs. ASPs that encourage compliance with 7 core components identified by the CDC have the potential to reduce AMR. In our study of all US states, we tested two hypotheses: (1) compliance with the CDC's ASP 7 core components would increase between 2014 and 2016 and (2) states with a higher percentage of compliance to CDC's 7 core components for ASPs will have significantly lower MRSA and *C. diff* rates. Our results show that there has been an increase in compliance with the CDC's 7 core components nationwide, which was associated with a decrease in *C. diff* infections. However, we did not find an association with MRSA infections.

Increased compliance with 7 core components

As hypothesized, compliance with the CDC's 7 core components for ASP increased in every US state from 2014-2016. Nationally, the proportion of hospitals that met the 7 core components increased from 39% in 2014[6] to 48% in 2015[49] and 64% in 2016[27]. Not surprisingly, increases in compliance were greater in states with lower compliance in the initial study period. Increases are mostly driven by recent national policies which encourage ASP to be implemented in all healthcare facilities, such as the National Action plan for combating antibiotic resistance[81], the ASP Guidelines by the Society for Healthcare

Epidemiology of America (SHEA)[82], and The Joint Commission Standards for Antimicrobial Stewardship[77,83].

Despite nationwide increases in ASP adoption, compliance varies regionally. States with a higher percentage of compliance are closer to the west or east coast as opposed to states in the center of the country[49]. Studies that had access to more granular data were able to identify that larger (>200 beds) and teaching hospitals were more likely to have all 7 core elements implemented[49,78,79]. The core component "Action" was the most commonly implemented, although that could encompass a range of different facility-specific activities. "Leadership Commitment", such as written support from administrators and ASP-related compensation, was the strongest predictor for a hospital meeting the 7 core components[49,79].

Implementing the 7 core components has been associated with up to a 10% decrease in antimicrobial use in a large healthcare system[84], but an ideal level of antimicrobial use in hospitals is not known. However, the decrease in antimicrobial use can certainly improve antimicrobial-related adverse events. With national support and local implementation of stewardship activities, the judicious use of antimicrobials can be achieved, and emergence of resistance can be contained.

ASP associated with decreased *C. diff* infections

As hypothesized, ASP compliance with CDC's Core Elements was associated with a significant decrease in *C. diff* SIR in 2016 relative to 2014. One reason for why we observe that effect in the interaction model only in 2016 is because of the recent increase in ASP compliance. Since ASP compliance increased in every state since 2014, we were able to detect an effect in 2016.

This result is consistent with previous studies conducted in single hospital settings[44,50,52]. The VA system also reported declining *C. diff* infection rates after implementing national stewardship activities[74]. A reduction in *C. diff* infections has been associated with decreased antibiotic prescribing in outpatient settings as well[47]. Restrictive and persuasive (e.g., audit and feedback) stewardship strategies were found to be more effective in decreasing *C. diff* rates[44,85–88].

Moreover, ASPs may sometimes include disease-specific policies, such as guidelines for treatment of *C. diff* infection, which recommend stopping unnecessary antimicrobials for any patient with *C. diff* infection[26,89]. Better clinical response and reduced risk of recurrence follow as a result[89,90] and may also explain the association between ASP and reduced *C. diff* rates in this study. In summary, our study results are consistent with evidence from single settings and other venues of healthcare.

No effect on MRSA infections

Our hypothesis was not supported for MRSA. Our study did not find evidence of an effect of ASP on MRSA infections. There are several possible explanations for this difference. First, resistant microorganisms such as MRSA take longer to respond to ASP changes than *C. diff* since the latter is more of an adverse event, so the 3-year period in our study may not have been sufficient to capture the effect on MRSA. Large, nationwide studies that found an effect of ASP on rates of MRSA or other resistant bacteria were 7-16 years long and were done outside of the US[91–93].

Second, resistant strains may also require higher levels of ASP compliance or specific restriction policies to impact their infection rates in hospitals. A systematic literature review found large variance in resistant microbe outcomes when assessing the impact of interventions to improve antibiotic prescribing[94]. Mixed results are likely explained by prevalence density of MRSA and intensity of the intervention in different studies[92].

As an example of varying ASP interventions, two international studies combined antimicrobial stewardship with hand hygiene interventions and detected a decline in several strains of MRSA[95,96]. Our general measure for ASP does not capture that level of granularity in stewardship activities to understand the effective components of those programs.

Limitations

There are several limitations in this study. First, we only had 3 years of state-level ASP data, which may have decreased our statistical power in the state-level analyses. Second, we only had access to percentage of hospitals that met all 7 CDC core elements, rather than the distribution of each specific element hospitals adopted and specific

stewardship activities at the hospital level. Therefore, we could not assess the impact of specific core elements on *C. diff* and MRSA rates. Moreover, because we lacked data on stewardship strategies, we had to use a more general measure for ASP in this study, which may not have enough granularity to understand its relationship with resistant infections.

Third, MRSA is an important and publicly available measure but may not be ideal to reflect changes in ASPs in the short term. MRSA is an endemic infection and may take several years to respond to improvements in antimicrobial prescribing practices. Finally, we are not be able to estimate causal relationships since there may be unmeasured residual confounders in the analyses. For example, patient safety programs in hospitals could have some overlap with the CDC's 7 core elements and impact resistant infections and *C. diff* rates as well, although that is somewhat controlled for by using a FE estimation.

Conclusion & Policy Implications

Our study found evidence of a positive impact of comprehensive ASPs on *C. diff* SIR in acute care hospitals. Even though compliance with the CDC's 7 Core Components has increased in all states nationwide, we did not find evidence of an impact on MRSA SIR, probably due to the short length of the study and variety of stewardship strategies that ASPs may implement.

This study has a number of policy implications. It provides a novel approach to estimating the effect of hospital ASP on infection outcomes nationwide and, therefore, important evidence to the incipient body of literature in the field. Furthermore, this research measures the impact of guideline-compliant ASPs (e.g., meeting CDC's 7 core components), which has not been done before and may provide an incentive for researchers, policy makers, payers, hospital administrators and healthcare providers to promote and adopt comprehensive ASPs.

Perhaps most importantly, our findings suggest that a nationwide policy to reduce AMR was successful in preventing *C. diff.* Different strategies or a longer time horizon may be required for resistant organisms. Policy makers can use insights from this study to advocate for ASP. Payers may also use evidence from this study to link comprehensive ASP

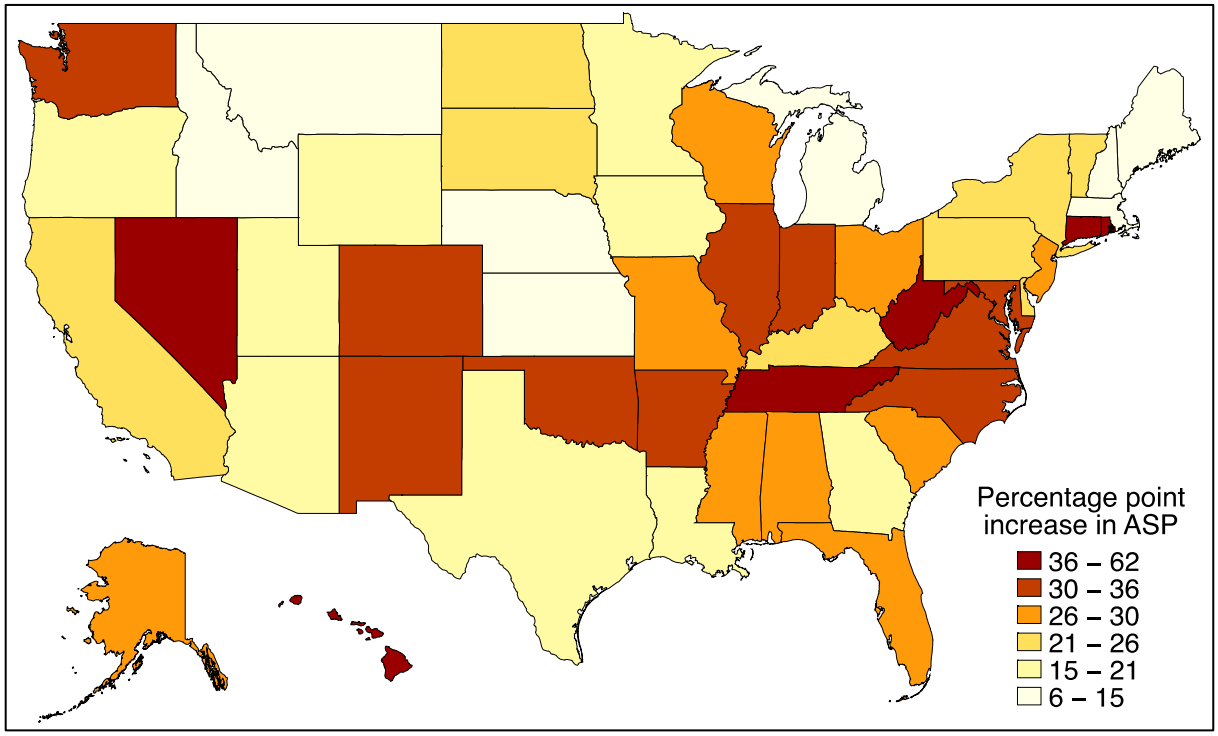
implementation to financial incentives or penalties for those hospitals with SIRs above a certain threshold.

At the healthcare setting level, administrators can use our results to leverage momentum for the local implementation of all components of hospital ASPs and education of healthcare personnel. Providers may use it for continued education and awareness of the importance of complying with hospital policies to promote the judicious use of antibiotics and control of infection and resistance rates.

The study of hospital ASPs would greatly benefit from more granular data on the components of ASP and type stewardship activities, especially if available at the hospital level. Researchers should seek mechanisms to make possible/facilitate obtaining such data from governmental health agencies. Since ASP data are available from 2014 on, future research will also benefit from longer follow up periods and possibly using other relevant microorganisms in addition to the ones used in this study.

Figures & Tables

Figure 4.1 Increase in Antimicrobial Stewardship Programs (ASP) meeting CDC's 7 core components in US hospitals by state, 2014-2016.



Baseline % ASP compliance in 2014:
States with <20% ASP compliance: DC, IA, ND, VT
States with 20-29% ASP compliance: AR, CO, CT, HI, KS, LA, MN, MO, MS, NH, OK, SD, TN, VT, WV, WY
States with 30-39% ASP compliance: AL, DE, IL, IN, KY, MT, NE, NM, OH, OR, RI, TX, WA, WI
States with 40-49% ASP compliance: AK, FL, GA, MI, NC, NJ, NV, PA, SC, VA
States with 50-59% ASP compliance: AZ, CA, ID, MA, MD, ME, NY, UT

Table 4.1 Descriptive statistics for MRSA[a] and *C. diff*[b] models, 2014-2016

Variable	**US states, 2014-2016 n=153 Mean/% (SD)**
MRSA SIR[c]	0.87 (0.29)
C. diff SIR	0.91 (0.14)
% ASP compliance in the state	48.1 (17.5)
Public	14.0%
Private for Profit	14.4%
Private Not for Profit	71.6%
Teaching	55.5%
Rural	17.5%
Bed Count	410 (126)
Quality Accredited	94.5%
Changes in ownership = 0	32.0%
Changes in ownership = 1	28.4%
Changes in ownership >1	39.6%
Compliant CMS[d] requirements	71.9%
Emergency Services	98.1%
% ICU[e] beds	7.6 (1.5)
Length of Stay (days)	3.6 (0.4)
ICU Services	92.1%
Patient Safety Index	0.92 (0.1)
% Hospital Readmissions	15.3 (0.6)

[a] methicillin-resistant *Staphylococcus aureus*
[b] *Clostridioides difficile*
[c] Standardized infection ratio
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit

Table 4.2 Regression-adjusted estimates for the association between %ASPs[a] meeting CDC's 7 core components and MRSA[b] SIRs[c], 2014-2017

MRSA MODELS	**State level**	**State level + interactions**	**State level + lagged x**
VARIABLE	***b(SE)***	***b(SE)***	***b(SE)***
%ASP COMPLIANCE	0 (0.002)	-0.001 (0.003)	
2015	0.075 (0.058)	0.002 (0.13)	
2016	0.098 (0.078)	0.05 (0.152)	-0.04 (0.041)
%ASP X 2015		0.002 (0.002)	
%ASP X 2016		0.001 (0.003)	
TEACHING	0.003 (0.648)	0.105 (0.636)	0.509 (0.737)
BED COUNT	-0.002 (0.002)	-0.003 (0.003)	0 (0.003)
QUALITY ACCREDITED	-0.486 (0.354)	-0.463 (0.369)	0.24 (0.47)
COMPLIANT WITH CMS[D] REQUIREMENTS	-0.311 (0.514)	-0.339 (0.507)	-0.307 (0.502)
% ICU[E] BEDS	-0.054 (0.063)	-0.059 (0.06)	-0.029 (0.048)
LENGTH OF STAY	0.134 (0.312)	0.109 (0.304)	-0.149 (0.15)
PATIENT SAFETY INDEX	-0.161 (0.285)	-0.126 (0.286)	-0.289 (0.249)
% HOSPITAL READMISSIONS	0.209 (0.115)	0.223 (0.123)	0.025 (0.096)
LAGGED %ASP			0.001 (0.002)
2017			-0.153* (0.07)
PUBLIC	-0.605 (1.087)	-0.488 (1.03)	1.528** (0.439)
PRIVATE FOR PROFIT	1.13 (0.632)	1.097 (0.659)	1.912 (0.965)
RURAL	0.062 (0.737)	-0.085 (0.656)	-0.258 (0.448)
CHANGES IN ONWERSHIP = 1	1.78 (1.412)	1.815 (1.467)	-0.369 (0.763)
CHANGES IN ONWERSHIP >1	-0.998 (1.929)	-0.984 (1.954)	-1.348 (1.343)
EMERGENCY SERVICES	0.749 (1.007)	0.748 (1.019)	-0.371 (0.5)
ICU SERVICES	-1.488 (1.516)	-1.198 (1.469)	0.247 (0.578)
CONSTANT	-0.26 (2.982)	-0.422 (3.114)	1.453 (2.157)
N	151	151	152
R^2	0.392	0.397	0.484

[a] Antimicrobial Stewardship Program
[b] methicillin-resistant *Staphylococcus aureus*
[c] Standardized infection ratio
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit
* p<0.05 ** p<0.01 *** p<0.001

Table 4.3 Regression-adjusted estimates for the association between %ASPs[a] meeting CDC's 7 core components and *C. diff*[b] SIRs[c], 2014-2017

C. DIFF MODELS	**State level**	**State level + interactions**	**State level + lagged x**
VARIABLE	***b(SE)***	***b(SE)***	***b(SE)***
%ASP COMPLIANCE	0.001 (0.001)	0.002 (0.001)	
2015	0.127*** (0.031)	0.174** (0.052)	
2016	0.110** (0.037)	0.309*** (0.062)	-0.026 (0.028)
%ASP X 2015		-0.001 (0.001)	
%ASP X 2016		-0.003*** (0.001)	
TEACHING	-0.315 (0.3)	-0.504 (0.282)	0.261 (0.341)
BED COUNT	0 (0.001)	0 (0.001)	0 (0.002)
QUALITY ACCREDITED	-0.111 (0.267)	-0.251 (0.232)	0.275 (0.322)
COMPLIANT WITH CMS[D] REQUIREMENTS	-0.201 (0.16)	-0.241 (0.129)	-0.096 (0.267)
% ICU[E] BEDS	-0.061* (0.027)	-0.062** (0.023)	-0.071*** (0.02)
LENGTH OF STAY	-0.241* (0.111)	-0.13 (0.096)	-0.179 (0.104)
PATIENT SAFETY INDEX	-0.474** (0.141)	-0.433** (0.151)	-0.325 (0.168)
% HOSPITAL READMISSIONS	0.066 (0.065)	0.038 (0.06)	-0.01 (0.056)
LAGGED %ASP			-0.001 (0.001)
2017			-0.08 (0.044)
PUBLIC	-0.714 (0.596)	-0.824 (0.567)	0.985* (0.418)
PRIVATE FOR PROFIT	0.32 (0.285)	0.258 (0.235)	0.295 (0.655)
RURAL	-0.271 (0.387)	-0.252 (0.305)	0.029 (0.374)
CHANGES IN ONWERSHIP = 1	-1.162 (0.977)	-1.504 (0.896)	0.409 (0.563)
CHANGES IN ONWERSHIP >1	-3.147** (1.165)	-3.003** (1.07)	0.309 (0.9)
EMERGENCY SERVICES	0.035 (0.467)	0.035 (0.3)	0.343 (0.345)
ICU SERVICES	-0.163 (0.703)	-0.413 (0.772)	1.082*** (0.263)
CONSTANT	3.765* (1.67)	4.480** (1.632)	0.417 (1.543)
N	151	151	152
R^2	0.667	0.72	0.803

[a] Antimicrobial Stewardship Program
[b] *Clostridioides difficile*
[c] Standardized infection ratios
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit
* p<0.05 ** p<0.01 *** p<0.001

CHAPTER 5. ARE RATES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND *CLOSTRIDIOIDES DIFFICILE* ASSOCIATED WITH QUALITY AND CLINICAL OUTCOMES IN US ACUTE CARE HOSPITALS?

Overview

Objective: Examine the association between rates of methicillin-resistant *Staphylococcus aureus* (MRSA)/*Clostridioides difficile* (*C. diff*) and quality and clinical outcomes in US acute care hospitals. **Population:** All Medicare-certified US acute care hospitals with *MRSA*/*C. diff* standardized infection ratio (SIR) data available from 2013-2017. **Data sources:** 2013-2017 hospital-level data from the Centers for Medicare & Medicaid Services' HospitalCompare, Provider of Service and Medicare Cost Reports data files. **Study design**: We estimated separate hospital and time fixed effects models for 30-day hospital readmissions, length of stay, 30-day mortality and days in the intensive care unit. The key explanatory variables were standardized infection ratios for MRSA and *C. diff*. **Principal findings:** We found no association of MRSA or *C. diff* rates with any of the four outcomes. **Conclusions**: Our null results add to the mixed evidence in the field. Some outcome measures may have not been appropriate because of different collection period and limited population represented. Moreover, there are likely residual confounding factors for each of the outcomes. Future research should use patient-level data and appropriate methods to guide prioritization of efforts to tackle antimicrobial resistance and continued education of providers at the hospital level.

Introduction

The widespread overuse and misuse of antimicrobials cause microorganisms to become resistant to treatment[63] and make patients susceptible to both resistant infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridioides difficile* (*C. diff*) infections. The latter is not technically a resistant bacteria but it thrives when the human microbiome is killed by antimicrobials. Antimicrobial resistance (AMR) is a growing problem in the US, affecting more than 2 million patients. MRSA invasive infections alone (not including wound, skin and soft tissue) impacted 119,000 patients in 2017, resulting in almost 20,000 deaths in the US[97]. Additionally, *C. diff* infections affected 453,000 patients, resulting in 29,000 deaths in 2011[98]. AMR and *C. diff* infections resulted $20 billion in direct healthcare costs and $35 billion in overall societal costs in 2013[1].

The global scenario is even more disturbing: by 2050, AMR could lead to 10 million deaths and cost $100 trillion dollars annually in direct costs and lost global production[99]. The Centers for Disease Control & Prevention (CDC) considers *C. diff* an “urgent” threat, and MRSA may quickly be upgraded from “serious” to “urgent” without ongoing monitoring and prevention strategies[1].

Hospitals are reservoirs for AMR because they combine patients who are either susceptible to, or already have, resistant pathogens, intensive/prolonged use of antimicrobials, and a risk of cross-infections[30]. Resistant microorganisms can impact clinical and quality outcomes in several ways. Patients infected with resistant pathogens are more likely to experience delays in the initiation of effective therapy[100], longer hospitalizations[101,102], surgery or other procedures, adverse outcomes (since their treatment often requires more toxic therapy)[103], clinical failure and recurrent infections[104]. Furthermore, infections that are resistant to all current available treatments have substantial mortality rates[103].

The incidence of bacterial infection during inpatient stays in the US is 20.1%. Of those infections, 10.8-16.9% are due to multidrug-resistant organisms (MRSA and *C. diff* included)[105]. Most AMR-related deaths occur in hospitals[1]. MRSA, *C. diff* and other

healthcare-associated infections (HAIs) are important measures that may reflect the quality of care and impact clinical outcomes in hospital settings[106,107]. In studies using patient-level data, compared to infections that are more susceptible to antibiotics, MRSA and *C. diff* infections require prolonged treatment, longer hospital stays, may result in more disability and deaths[1,108,109], higher healthcare in-hospital and outpatient costs[1,105,109,110], and high economic burden in terms of productivity losses due to absence from work or death[109].

A comprehensive picture of the prevalence, incidence, mortality and cost of AMR remains elusive[1,103,111]. Studies on the burden and consequences of AMR suffer from heterogeneity in setting, sample size, type of pathogen/resistance, outcome measures and methods[73,104,111,112]. Although studies show a greater risk of death for patients with antibiotic-resistant infections compared to susceptible infections, better estimates of that differential risk are needed[1,112,113]. Therefore, our objective was to examine the association between rates of MRSA/*C. diff* and quality and clinical outcomes in acute care hospitals in the US. We hypothesized that higher rates of MRSA and *C. diff* in acute care hospitals are related to higher rates of 30-day hospital readmissions, 30-day mortality, longer length of hospital stay and more intensive care unit (ICU) days in US hospitals.

Methods

Data Sources

We merged 2013-2017 hospital-level data from the Centers for Medicare & Medicaid Services' (CMS) HospitalCompare, Provider of Service File and Medicare Cost Reports data files. HospitalCompare includes quality of care information from over 4,000 Medicare-certified hospitals; the Provider of Service Files contain hospital characteristics and type of services provided; and Medicare Cost Reports include utilization and cost data as well as facility characteristics for all Medicare-certified providers.

Subjects

The study population included all Medicare-certified US acute care hospitals for which MRSA/*C. diff* standardized infection ratio (SIR) data were available from 2013-2017. The National Healthcare Safety Network (NHSN) does not calculate SIR for hospitals with

<1 expected infection, therefore, we excluded those hospitals (Appendix B.1). Veteran Affairs (VA), children's and critical access hospitals were excluded because of different data collection periods, different case mix/hospital epidemiology and lack of reporting requirements for infection data, respectively.

Measures

Table 5.1 contains detailed operational definitions for each variable. Our four outcomes were: 30-day hospital readmissions, calculated as the percentage of patients re-admitted to the hospital within 30 days of discharge (Medicare beneficiaries only, adjusted for patient characteristics); length of stay (LoS), calculated as the mean length of inpatient days; 30-day mortality, calculated as the weighted average of 30-day mortality for chronic obstructive pulmonary disease, heart attack, heart failure, pneumonia and stroke based on proportion of hospital stays for each diagnosis[114] (included Medicare beneficiaries only and is adjusted for patient characteristics); and ICU days, measured as the total number of inpatient days spent in the ICU.

Our two main regressors were: MRSA SIR (ratio of MRSA bacteremia laboratory-identified events to the predicted number of MRSA bacteremia events) and *C. diff* SIR (ratio of *C. diff* laboratory-identified events to the predicted number of *C. diff* events). SIRs were calculated for each hospital by the CDC's NHSN and made available through HospitalCompare's data system. MRSA predicted events were calculated by the NHSN based on admission for prevalence rate of MRSA infections, average length of stay, medical school affiliation, type of hospital, number of ICU beds, and amount of MRSA infections identified in the emergency department and/or observation units. *C. diff* predicted events were calculated using type of laboratory test used to identify infection, whether the hospital has emergency departments and/or observation units that collect stool specimens for testing, facility bed size, number of ICU beds, medical school affiliation, admission prevalence rate of *C. diff* infections, and type of hospital. The MRSA/*C. diff* SIR was calculated only for hospitals with at least one predicted event[39].

Analysis

We estimated linear hospital and time fixed effects (FE) models for each of our four outcomes (30-day hospital readmissions, length of stay, 30-day mortality and ICU days). We chose FE because it controls for unmeasured and measured time-invariant confounders at the hospital level such as location, hospital type, hospital ownership, population served, structure for quality improvement and infection control. Although some of these characteristics may not be completely time-invariant, we believe they are largely time-invariant.

For each outcome we ran two models, one with MRSA SIR as the main regressor and one with *C. diff* SIR as the main regressor. We controlled for the time-variant characteristics listed in Table 5.1. Standard errors were clustered at the state level and the analyses were weighted by hospital size. We confirmed the FE specification by using a Hausman test between FE and random effects estimation for each model.

As sensitivity analyses, we added two other HAIs in the models that may be related to both MRSA/*C. diff* infections and quality and clinical patient outcomes: central line-associated blood stream infection (CLABSI) and catheter-associated urinary tract infection (CAUTI).

Results

In the models where MRSA was the key explanatory variable, the number of hospitals with available data from 2013 to 2017 was 2,016 (30-day readmission), 2,023 (LoS), 1,907 (30-day mortality) and 1,920 (ICU days). When *C. diff* was the key explanatory variable, the number of hospitals with available data was 3,163 hospitals (30-day readmission), 3,177 (LoS), 2,427 (30-day mortality) and 2,774 (ICU days). Characteristics of hospitals for the MRSA and *C. diff* models are presented in Table 5.1.

In the MRSA models, MRSA SIR was not associated with any of the four outcomes: 30-day hospital readmissions, LoS, 30-day mortality or ICU days (Table 5.2). Similarly, in the *C. diff* models, *C. diff* SIR was also not significantly associated with any of the outcomes (Table 5.3). The year intercepts were mostly negatively associated with 30-day readmissions

and positively associated with LoS, 30-day mortality and ICU days in both MRSA and *C. diff* models. A few control variables were significant as well. For example, teaching status was positively associated with 30-day readmissions. Patient Safety Indicator (lower scores reflect higher quality) was positively associated with 30-day mortality in both models as well (Tables 5.2 and 5.3). Results were robust to the inclusion of CLABSI and CAUTI control variables (Appendices B.1-B.3).

Discussion

The increasing prevalence of AMR among hospitalized patients in the US and around the world has been associated with worse patient outcomes (including death), higher health care utilization, and greater health care costs in patient-level analysis. Using a national sample of US acute care hospitals, we tested the hypothesis that higher rates of MRSA and *C. diff* were associated with higher rates of 30-day hospital readmissions, 30-day mortality, longer length of hospital stay and more ICU days in US hospitals. Our findings did not support any of these hypotheses. Other studies comparing quality and clinical outcomes for patients with MRSA, *C. diff* or other AMR used patient-level data and were highly heterogeneous in terms of setting, methods, comparators and outcomes. They have found mixed results for the proposed relationships. Single setting studies and specific comparators may have contributed with internal consistency in studies where the difference in outcomes were significant.

30-day readmissions

Persistence of colonization in patients with previous MRSA and other infections is common and may last from 5 months to two years after their last discharge[115,116]. Around 61.6% of patients with AMR are readmitted to the hospital within one year of discharge[117]. However, previous studies show high heterogeneity and conflicting results on the effect of MRSA on readmissions. A nationwide study using the readmissions database found that 48.5% of patients with *Staphylococcus aureus* bacteremia had MRSA bacteremia. Overall 30-day readmission was 22% with no difference for MRSA patients. However, MRSA had more readmissions for bacteremia recurrence[118]. Several other studies showed that MRSA

had no statistical significance on readmissions[119,120]. However, patients isolated because of MRSA had 4.4% higher 30-day readmissions compared to other patients[121]. In international settings, the results were also inconsistent. A study in Australia comparing patients with MRSA and susceptible *S. aureus* found no difference in hospital readmissions[122]. But in Spain, 30-day readmission was 2.2 times higher in patients with HAIs caused by resistant pathogens[123].

Recurrence rates for healthcare-associated *C. diff* infection have been found to be as large as 50%[124,125], which increases the chance of a return to the hospital. In a single-setting study, 27% of patients with a *C. diff* infection had at least one complication and 20% were re-admitted to the hospital[126]. In a larger study, *C. diff* was also associated with high burden on hospital readmissions[127]. However, other studies did not show such a high burden[128].

In a retrospective cohort study, patients carrying MRSA or *C. diff* after discharge were more likely to be readmitted to a hospital or nursing home compared to non-carriers, exposing other facilities to the spread of AMR organisms[129]. A nationwide study in France identified history of *C. diff* infection as an independent predictor of 90-day hospital readmissions[130]. However, in a Medicare sample, the effect of *C. diff* on readmissions depended on treatment prescribed at discharge[131], a factor not considered in most of studies looking at this relationship. In light of the body of literature, our study results are not surprising given the highly mixed results from previous investigations.

Length of stay

A similar pattern is observed in studies assessing the impact of MRSA or *C. diff* on length of hospital stay in terms of heterogeneity in settings, methods and outcomes; however, the significance of previous studies was mostly consistent across them, despite contrasting with our results. One reason for our null results is that we used hospital-level analysis as opposed to patient-level analysis, commonly used in previous studies.

A large study showed that 18% of patients were diagnosed with *C. diff* infections with average LoS of 13.6 days[128]. Several studies showed that *C. diff* and MRSA were associated with longer hospital stays[129,132]. A nationwide study using the readmissions database,

showed that patients with MRSA had longer hospitalization[118]. Patients with MRSA surgical infections also had greater LoS than patients[120,133]. However, a single setting study found no difference in LoS for patients with resistant infections[123].

The extent to which resistant infections increased LoS also varies across studies. Patients with MRSA stayed 30% longer in the hospital and had 43% higher cost of care[121]. Another study found that patients with MRSA had, on average, an 8-day longer hospital stay[119]. Despite consistent results from other studies, an important factor that was not addressed in any of them is reverse causation. Patients with longer LoS are exposed to resistant pathogens for longer and, therefore, are more likely to acquire MRSA, *C. diff* or other HAIs, which could also explain the significant results in these studies. In contrast, our results did not find a significant association likely because we used hospital-level data, as opposed to patient-level data.

30-day mortality

Contrary to our null results, several previous studies found MRSA and *C. diff* to be significantly associated with 30-day mortality. Studies related to MRSA were less consistent than those addressing *C. diff*, which could again be explained by the settings and methods used.

A single setting study estimated that AMR might cause more than 40% of deaths among patients with resistant HAIs and that 30-day mortality was 1.7 times higher in patients with resistant pathogens[123]. For patients with blood stream MRSA infections, 30-day mortality was 16%[134]. In nationally representative studies of US hospitals, mortality rates related to MRSA bacteremia were higher than for susceptible *S. aureus*[108,118]. However, MRSA had no difference in mortality among surgical patients[120] or patients isolated because of MRSA[121]. A long-term cohort study in Australia also did not find any difference in mortality among patients with MRSA[122].

Fewer studies on the impact of *C. diff* were available. An important gap in the literature given that 9.3% of patients die within 30 days of *C. diff* diagnosis[98]. A large study found that around 13% of hospital patients had nosocomial *C. diff* infections, 15.2% of those

died and 1.5% died directly or indirectly of *C. diff*[128]. A meta-analysis found *C. diff* to be associated with higher mortality rates compared to patients without *C.diff*[132]*. C. diff* was also associated with higher mortality in patients with hospital-acquired pneumonia[135].

Mortality due to AMR is hard to attribute[1,135]. Currently, there are not specific criteria or algorithms to link deaths directly to AMR, ruling out a co-existing illness/condition. Studies trying to measure attributable mortality rely on a subjective judgment to distinguish when AMR is directly the cause of death, or is contributing or merely related to the death, especially in hospital settings where patients tend to accumulate other complications[1]. As an example, a meta-analysis showed that 23% of the included studies found significantly higher mortality associated with MRSA bacteremia, while 77% did not find significant results. There was significant heterogeneity across the studies due to different estimation methods, adjustment for confounders and severity of illness, higher proportion of nosocomial infections versus community-acquired infections, source of infections and mortality outcomes[113].

ICU days

Our results are not surprising compared to the current literature. Studies on the impact of MRSA and *C. diff* on ICU days had mixed results and were also very different in terms of methods, setting and patient population. In a long study with pediatric patients, MRSA bacteremia resulted in more ICU admissions[136]. But in a single setting study, resistant HAI infections were not associated with more ICU admissions[123]. In international settings, MRSA patients required more ICU care, however, the ICU stay was not longer for MRSA patients[137]. On the other hand, another study showed that MRSA patients had significantly longer ICU stay compared to other patients[138]. However, these results may not be reliable because important confounders were not addressed.

C. diff had higher incidence in ICUs[139,140] and a meta-analysis found it to be associated with longer ICU stays compared to patients without *C.diff*[132]*.* However, similar to the LoS outcome, results are not reliable without properly addressing reverse causation, since longer exposure to intensive care may greatly increase the chances of developing *C. diff* and AMR.

Most of the cited studies analyze the impact of AMR/*C. diff* on in-hospital outcomes but the hospital perspective is far from a complete picture of the real impact of AMR on healthcare and patient outcomes since an important proportion of the care is delivered in rehabilitation facilities, nursing homes or even at home. However, access to data from those sites is limited[103].

Limitations

This study has several limitations. First, we used hospital and time FE to control for important confounders but in light of the null results, we may have not had enough within hospital variation left to detect differences in our outcomes since this is a consistent but inefficient method. Moreover, we are only able to estimate associations and not causal relationships, especially in the LoS and ICU days models, where reverse causation is likely. Our data did not allow for the use of appropriate instrumental or lagged variables because the latter would require a shorter time period variable.

A second limitation may have been the definition of some of our outcomes. Most variables in this study were collected from January through December, but 30-day readmissions and 30-day mortality were collected from July through June of each year. The 30-day mortality variable also includes only patients who had one of 5 relevant diagnoses and is a 3-year moving average from July to June. These measures may not have been good enough to capture the outcome that we intended to analyze because of the different timeframe and limited representation of patients. Third, there may be tautological correlation between MRSA/*C. diff* SIR and LoS since LoS is included in the SIRs calculation, although older data was used.

Conclusions & Policy Implications

This study did not find associations between MRSA and *C. diff* and our four outcome measures: 30-day readmissions, 30-day mortality, length of stay and ICU days. Given the mixed results in the current literature, our findings likely reflect the complexity of the task of assessing quality and clinical outcomes in the hospital context. Our study highlights the need for more publicly available infection data from hospitals. We recognize that patient-level

infection data are sensitive since it reflects hospital performance, but such data are needed to understand the relationship between AMR and outcomes that are important to patients, providers, and health care systems.

Although we did not find statistically significant associations, comprehending the impact of resistant infections on quality and clinical outcomes remains very relevant for payers and policymakers as they make funding decisions regarding programs to control and prevent the emergence of AMR. Results from this study may help develop the foundation for future studies. Future research should use larger samples of patient-level data and test the effect of different resistant microorganisms in relevant patient groups or healthcare settings. It is also paramount that future research use appropriate methods to control for confounders at the patient, hospital and regional level, as well as for reverse causation. As a result, reliable evidence will guide future prioritization of efforts to tackle AMR and continued education of providers at the hospital level.

Tables

Table 5.1 Descriptive statistics for models where MRSA[a] or *C. diff*[b] are the explanatory variable, 2013-2017

Variable	**MRSA Models n=8,806 Mean/% (SD)**	**C. diff Models n=14,590 Mean/% (SD)**
MRSA SIR[c]	0.93 (0.80)	
C. diff SIR		0.84 (0.50)
% 30-Day Hospital Readmissions	15.5 (1.03)	15.4 (0.96)
Length of Stay (days)	3.65 (0.71)	3.41 (0.85)
% 30-Day Mortality	12.4 (1.30)	12.5 (1.28)
ICU[d] Days	7209 (6609)	5143 (5980)
Public	12.8%	14.9%
Private For Profit	17.5%	20.4%
Private Not For Profit	69.7%	64.6%
Teaching	48.2%	35.5%
Rural	8.5%	24.6%
Bed Count	368 (250)	263 (236)
Quality Accredited	97.9%	93.5%
Changes in ownership = 0	29.8%	32.2%
Changes in ownership = 1	32.6%	30.9%
Changes in ownership >1	37.6%	36.9%
Compliant with CMS[e] Requirements	73.6%	75.8%
Emergency Services	98.1%	96.4%
% ICU beds	8.3 (5.40)	8.1 (5.83)
ICU Services	93.2%	88.5%
Patient Safety Index	0.92 (0.22)	0.91 (0.20)

[a] Methicillin-resistant *Staphylococcus aureus*
[b] *Clostridioides difficile*
[c] Standardized infection ratio
[d] Intensive Care Unit
[e] Centers for Medicare and Medicaid Services

Table 5.2 Regression-adjusted estimates for the association between MRSA[a] SIR[b] and quality and clinical outcomes in acute care hospitals, 2013-2017

	30-Day Hospital Readmissions	**Length of Stay**	**30-Day Mortality**	**ICU[c] Days**
	b(SE)	**b(SE)**	**b(SE)**	**b(SE)**
MRSA SIR	0.010	0.008	0.006	23.169
	(0.009)	(0.006)	(0.009)	(50.409)
Teaching	0.131*	-0.030	0.060	715.873
	(0.064)	(0.031)	(0.053)	(517.922)
Bed Count	-0.000	0.001	-0.000	9.463***
	(0.000)	(0.000)	(0.000)	(1.534)
Quality Accredited	0.159	0.063	0.068	302.271
	(0.086)	(0.033)	(0.117)	(225.535)
Changes in Ownership = 1	0.071	0.023	-0.063	-495.347
	(0.181)	(0.071)	(0.157)	(315.908)
Changes in Ownership > 1	-0.173	0.044	-0.078	-1.3e+03*
	(0.232)	(0.083)	(0.200)	(493.947)
Compliant with CMS[d] Requirements	0.031	-0.008	-0.005	249.671
	(0.068)	(0.037)	(0.049)	(310.300)
%ICU Beds	0.004	-0.012**	-0.004	526.651***
	(0.004)	(0.004)	(0.004)	(90.957)
Patient Safety Indicator	0.058	-0.036	0.236**	-126.074
	(0.051)	(0.026)	(0.069)	(273.857)
2014	-0.321***	0.028**	-0.322***	186.273**
	(0.041)	(0.009)	(0.014)	(69.267)
2015	0.005	0.044**	1.149***	508.058**
	(0.056)	(0.014)	(0.027)	(147.838)
2016	-0.297***	0.040*	0.832***	686.847***
	(0.060)	(0.019)	(0.036)	(137.506)
2017	-0.299***	0.014	0.734***	661.687***
	(0.058)	(0.024)	(0.040)	(162.552)
Constant	15.683***	3.453***	11.873***	159.835
	(0.215)	(0.268)	(0.292)	(1408.455)
N	8754	8606	8284	8149
r2	0.094	0.020	0.630	0.136

[a] Methicillin-resistant *Staphylococcus aureus*
[b] Standardized infection ratio
[c] Intensive Care Unit
[d] Centers for Medicare and Medicaid Services
* p<0.05
** p<0.01
*** p<0.001

Table 5.3 Regression-adjusted estimates for the association between *C.diff*[a] SIR[b] and quality and clinical outcomes in acute care hospitals, 2013-2017

	30-Day Hospital Readmissions	**Length of Stay**	**30-Day Mortality**	**ICU[c] Days**
	b(SE)	**b(SE)**	**b(SE)**	**b(SE)**
C. diff SIR	0.011	0.011	0.032	-6.235
	(0.020)	(0.009)	(0.024)	(91.543)
Teaching	0.114*	-0.014	0.048	573.619
	(0.054)	(0.028)	(0.045)	(443.620)
Bed Count	-0.000	0.001	-0.000	8.759***
	(0.000)	(0.000)	(0.000)	(1.526)
Quality Accredited	0.152*	-0.002	0.057	239.238
	(0.071)	(0.051)	(0.104)	(186.313)
Changes in Ownership = 1	-0.018	-0.005	-0.054	-288.488
	(0.138)	(0.060)	(0.126)	(267.487)
Changes in Ownership > 1	-0.176	-0.021	-0.075	-772.757
	(0.188)	(0.074)	(0.186)	(404.254)
Compliant with CMS[d] Requirements	0.026	0.012	0.001	226.325
	(0.059)	(0.033)	(0.046)	(277.968)
%ICU Beds	0.004	-0.012**	-0.002	425.281***
	(0.003)	(0.004)	(0.005)	(76.091)
Patient Safety Indicator	0.045	-0.031	0.214***	-140.534
	(0.048)	(0.026)	(0.061)	(254.130)
2014	-0.337***	0.026**	-0.332***	165.174**
	(0.036)	(0.008)	(0.013)	(59.577)
2015	-0.006	0.034*	1.143***	457.263***
	(0.051)	(0.013)	(0.025)	(129.835)
2016	-0.298***	0.026	0.826***	604.467***
	(0.051)	(0.018)	(0.034)	(120.523)
2017	-0.298***	0.002	0.739***	570.390***
	(0.050)	(0.020)	(0.036)	(136.953)
Constant	15.673***	3.485***	11.899***	639.801
	(0.170)	(0.262)	(0.281)	(1191.931)
N	14499	14300	11055	12814
r2	0.094	0.015	0.624	0.114

[a] *Clostridioides difficile*
[b] Standardized infection ratios
[c] Intensive Care Unit
[d] Centers for Medicare and Medicaid Services
* p<0.05
** p<0.01
*** p<0.001

CHAPTER 6. SUMMARY OF FINDINGS AND POLICY IMPLICATIONS

Each year, two million Americans acquire serious infections caused by bacteria that are resistant to antibiotics resulting in significant morbidity, mortality, health care utilization, and costs. This study addressed the persistent problem of AMR and other consequences of the injudicious use of antimicrobials by analyzing state and national programs designed to tackle AMR emergence. We also investigated implications of MRSA and *C. diff* infections for healthcare quality and clinical outcomes. This work is motivated by the unchecked growth of resistance in the US and across the world and the local, state and national initiatives to contain AMR and, ultimately, improve healthcare quality and patient outcomes.

This research involved three aims. In aim 1, we hypothesized that after the passage of a California mandate in 2015, MRSA and *C. diff* rates in acute care hospitals decreased more in California hospitals compared to other states. In aim 2, we hypothesized that compliance with the CDC's ASP 7 core components would increase between 2014 and 2016 in the US, and hospitals in states with a higher percentage of compliance to CDC's 7 core components for ASPs would have significantly lower MRSA and *C. diff* rates. In aim 3, our hypothesis was that higher rates of MRSA and *C. diff* in acute care hospitals would be related to higher rates of 30-day hospital readmissions, 30-day mortality, longer length of stay and more ICU days in US hospitals.

Summary of Findings

In all three aims we chose FE estimation methods based on theory and confirmed our choice using specification tests. In all aims our sample included hospitals for which MRSA/*C. diff* SIR were available, which excluded hospitals with expected number of infections smaller than one. Even though that causes our sample to decrease, it contributes for better internal consistency since the excluded hospitals are vastly different than the ones with at least one expected infection. We found significant results on the impact of hospital

ASP on MRSA and *C. diff* rates in aims 1 and 2, but no evidence of an association between MRSA/*C. diff* and quality and clinical outcomes in aim 3.

In aim 1, compared to hospitals in other states, California hospitals had a lower average MRSA SIR (0.79 versus 0.94) and *C. diff* SIR (1.01 versus 0.77). After the mandate, California hospitals had significant ($p<0.05$) increases of 23%, 30%, and 20% in MRSA infections in 2015, 2016 and 2017, respectively. Relative to other states, California hospitals also had a 20% ($p<0.001$) decrease in their *C. diff* SIR, but only in 2017. Although we were unable to control for all time-variant confounders, most confounding factors would bias the estimates towards the null (e.g., other ASP initiatives being adopted in the comparison group); thus, we may have underestimated the effect. However, despite evidence of a parallel trend in both MRSA and *C. diff* models, this assumption may not hold given the short panel data and our inability to verify trends before 2013.

In aim 2, the percentage of hospitals meeting the CDC's 7 core components for ASP between 2014 and 2016 increased in all states. A one percentage point increase in ASP compliance was associated with a 0.3% decrease ($p<0.01$) in *C. diff* infections in 2016 relative to 2014. Despite the numerically small effect only in the *C. diff* model, extrapolating would lead to large increases in ASP compliance observed in the real world. For example, a 10-percentage point increase in ASP compliance at the state level would be associated with a 3% decrease in *C. diff* infections, which represents a significant change.

We did not find an effect of ASP on MRSA SIR. One explanation may be that we only had 3 years of state-level ASP data, which severely limited our analysis. Moreover, our ASP data consisted of whether or not a hospital met the 7 core elements of ASP, so we were unable to assess specific elements which could affect infection rates. For example, if the "leadership" or "action" element are the ones with higher impact, our analysis may have been confounded by hospitals that did meet those elements but were not compliant with all the 7 core elements. These limitations may also explain the smaller/null impact relative to aim 1. Additionally, in Aim 1, we had more clearly defined requirements for hospitals from

California, as well as needing to comply with federal guidelines, which probably resulted in less variation across the actions that the hospitals were taking in order to comply.

In aim 3, we did not find evidence of an association between MRSA/*C. diff* and 30-day readmissions, length of stay, 30-day mortality and ICU days. The FE estimation may have contributed to a possible lack of variation to estimate the effects, (e.g., variation left after accounting for hospital and time FE in the models). Additionally, some outcomes such as 30-day readmissions and 30-day mortality may not have been good measures because of the different time period and limited diagnoses included in the 30-day mortality variable. We were also unable to examine reverse causation in the length of stay and ICU days models. Previous literature in the field presented high heterogeneity and mixed results, especially in studies examining 30-day readmissions, 30-day mortality and ICU days.

Implications for Practice and Policy

Overall, our results contribute to a better understanding of how ASPs can impact MRSA and *C. diff* infections and, in turn, how those infections can impact care in US acute hospitals. Our results also provide reliable evidence on the effectiveness of hospital ASPs for decision-makers to shape policy at various levels of the healthcare system.

By analyzing a statewide natural experiment in California, we were able to begin to unpack the relationship between a statewide ASP mandate and AMR rates for MRSA and *C. diff*. We were also be able to understand how those rates responded to the passage of the bill, e.g., time gap between mandate and actual decrease in infections. This understanding is important because it addresses a question for policy-makers who are considering a hospital ASP mandate with minimum requirements in their state.

We also provide a timely and new assessment of the impact of hospital ASPs that meet the CDC's 7 core elements, which may be used to inform future ASPs and strategies as we provide estimates of the association between the CDC's 7 core elements and common resistant infections. Therefore, this investigation not only adds to the bulk of literature, but also addresses important knowledge gaps.

In addition, we provide more detailed evidence on the association between relevant infections (MRSA and *C. diff*) and quality and clinical outcomes. Although our initial intent was to be able to discern which pathogen has a greater impact on the selected outcomes, the absence of evidence, along with mixed results from previous literature, suggest that these relationships are complex and need better data to better understand hospital care in the context of resistant infections. Armed with better data and reliable evidence, providers, policy-makers and healthcare administrators will be able to prioritize specific microorganisms in their ASPs.

Future Research

This investigation contributes to our understanding of ASPs; however, more research is needed. First, we may need to focus on the effect of specific elements of ASPs rather than using general measures as we did in this study, which would yield in cleaner analyses. Second, it may be useful to generate estimates of the pathways and mediating factors between ASPs, infection rates and patient outcomes. Although a more detailed investigation of this relationship would require a richer dataset with more granular ASP information.

Third, Missouri recently passed an ASP bill that was different from California's in several ways. Researchers should examine the implementation of this mandate to understand the impact of a less specific ASP mandate on resistant infections. Moreover, the Missouri mandate was passed after the announcement of the Joint Commission (JC) ASP requirements in 2016. Therefore, its investigation would add to the body of the literature in terms of the marginal benefit to the JC requirements.

Finally, besides comprehending more granular aspects of ASPs, research is needed to understand their specific effect on other relevant resistant bacteria as well. As carbapenem-resistant *Enterobacteriaceae* becomes reportable in more states, it should become the target of studies on the effect of ASP. Healthcare providers and administrators would also profit from studies on ASP implementation, such as ASP types and characteristics that are easier to enforce and identification of provider characteristics that are associated with higher compliance with ASP policies.

As we move forward in the study of the relationships around AMR, we will likely enhance research strategies and analytical methods with the increasing bulk of literature, allowing for better evidence and better decision-making in the field. With reliable estimates, future studies could use cost-effectiveness models to understand the benefit of implementing certain ASP strategies to a wider population. Accessing more granular data, such as the CDC's NHSN Annual Hospital Survey, which contain ASP information at the hospital level, would also be a step in that direction since it would allow for the development of a better statistical plan than was possible in this research. As we contribute to the knowledge in this area, we hope that the competent authorities will facilitate access to the needed data.

APPENDIX A: CHAPTER 4 SUPPLEMENTAL TABLES

Appendix Table A.1 Descriptive statistics for hospital-level MRSA[a] and *C. diff*[b] models, 2014-2016

Variable	**MRSA Model n=5,194 Mean/% (SD)**	**C. diff Model N=8,611 Mean/% (SD)**
MRSA SIR	0.95 (0.81)	
C. diff SIR		0.88 (0.50)
% ASP compliance in the state	53.3 (15.71)	52.1 (15.96)
Public	12.9%	14.8%
Private for Profit	17.6%	20.5%
Private Not for Profit	69.5%	64.7%
Teaching	48.6%	35.8%
Rural	8.5%	24.5%
Bed Count	370 (251)	265 (237)
Quality Accredited	97.9%	93.6%
Changes in ownership = 0	29.6%	32.0%
Changes in ownership = 1	32.7%	31.0%
Changes in ownership >1	37.7%	37.0%
Compliant CMS[c] requirements	73.0%	75.3%
Emergency Services	98.6%	96.9%
% ICU[d] beds	8.5 (5.28)	8.3 (5.76)
Length of Stay (days)	3.66 (0.73)	3.43 (0.88)
ICU Services	94.9%	90.4%
Patient Safety Index	0.91 (0.21)	0.90 (0.19)
% Hospital Readmissions	15.5 (1.01)	15.4 (0.95)

[a] methicillin-resistant *Staphylococcus aureus*
[b] *Clostridioides difficile*
[c] Centers for Medicare and Medicaid Services
[d] Intensive Care Unit
[e] Standardized infection ratio

Appendix Table A.2 Hospital-level regression-adjusted estimates for the association between %ASPs[a] meeting CDC's 7 core components and MRSA[b] SIRs[c], 2014-2017

MRSA MODELS	**Hospital level**	**Hospital level + interactions**	**Hospital level + lagged x**
VARIABLE	***b(SE)***	***b(SE)***	***b(SE)***
%ASP COMPLIANCE	0.001 (0.002)	-0.001 (0.003)	
2015	0.115*** (0.03)	-0.012 (0.093)	
2016	0.052 (0.055)	-0.042 (0.132)	-0.084*** (0.023)
%ASP X 2015		0.003 (0.002)	
%ASP X 2016		0.002 (0.003)	
TEACHING	-0.084 (0.073)	-0.082 (0.073)	-0.081 (0.09)
BED COUNT	0 (0.001)	0 (0.001)	0 (0.001)
QUALITY ACCREDITED	0.208 (0.11)	0.208 (0.111)	0.047 (0.121)
CHANGES IN ONWERSHIP = 1	-0.175 (0.289)	-0.179 (0.29)	-0.017 (0.096)
CHANGES IN ONWERSHIP >1	-0.212 (0.373)	-0.219 (0.377)	-0.053 (0.204)
COMPLIANT WITH CMS[D] REQUIREMENTS	-0.002 (0.035)	-0.001 (0.035)	0.013 (0.055)
% ICU[E] BEDS	-0.020* (0.009)	-0.020* (0.009)	-0.013 (0.01)
LENGTH OF STAY	0.103** (0.036)	0.102** (0.036)	0.065 (0.049)
PATIENT SAFETY INDEX	-0.021 (0.059)	-0.02 (0.059)	-0.099 (0.052)
% HOSPITAL READMISSIONS	0.02 (0.019)	0.021 (0.019)	-0.031 (0.022)
LAGGED %ASP			0.002 (0.002)
2017			-0.192*** (0.049)
CONSTANT	0.286 (0.651)	0.363 (0.651)	1.291 (0.657)
N	5194	5194	4861
R^2	0.016	0.017	0.016

[a] Antimicrobial Stewardship Program
[b] methicillin-resistant *Staphylococcus aureus*
[c] Standardized infection ratio
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit
* p<0.05
** p<0.01
*** p<0.001

Appendix Table A.3 Hospital-level regression-adjusted estimates for the association between %ASPs[a] meeting CDC's 7 core components and *C. diff*[b] SIRs[c], 2014-2017

C. DIFF MODELS	**Hospital level**	**Hospital level + interactions**	**Hospital level + lagged x**
VARIABLE	***b(SE)***	***b(SE)***	***b(SE)***
%ASP COMPLIANCE	0 (0.001)	0.001 (0.001)	
2015	0.091*** (0.013)	0.108** (0.035)	
2016	0.016 (0.025)	0.175** (0.058)	-0.075*** (0.016)
%ASP X 2015		0 (0.001)	
%ASP X 2016		-0.003** (0.001)	
TEACHING	-0.082** (0.03)	-0.086** (0.03)	-0.04 (0.031)
BED COUNT	0 (0)	0 (0)	0.001* (0)
QUALITY ACCREDITED	-0.025 (0.058)	-0.031 (0.056)	-0.038 (0.079)
CHANGES IN ONWERSHIP = 1	0.021 (0.084)	0.019 (0.082)	0.120* (0.05)
CHANGES IN ONWERSHIP >1	-0.09 (0.113)	-0.087 (0.113)	0.236** (0.075)
COMPLIANT WITH CMS[D] REQUIREMENTS	0.014 (0.031)	0.013 (0.03)	-0.038 (0.034)
% ICU[E] BEDS	0.007 (0.004)	0.007 (0.004)	0.008* (0.003)
LENGTH OF STAY	0.006 (0.018)	0.009 (0.018)	0.006 (0.02)
PATIENT SAFETY INDEX	-0.01 (0.029)	-0.009 (0.03)	0.013 (0.034)
% HOSPITAL READMISSIONS	0.003 (0.006)	0.002 (0.006)	-0.004 (0.007)
LAGGED %ASP			0 (0.001)
2017			-0.183*** (0.046)
CONSTANT	0.830*** (0.168)	0.818*** (0.178)	0.669** (0.197)
N	8611	8611	8225
R^2	0.031	0.034	0.099

[a] Antimicrobial Stewardship Program
[b] *Clostridioides difficile*
[c] Standardized infection ratios
[d] Centers for Medicare and Medicaid Services
[e] Intensive Care Unit
* p<0.05
** p<0.01
*** p<0.001

APPENDIX B: CHAPTER 5 SUPPLEMENTAL TABLES

Appendix Table B.1 Descriptive statistics for hospitals not included in the models where MRSA[a] or *C. diff*[b] were the explanatory variable, 2013-2017.

Variable	**Hospitals with MRSA SIR missing (2013-17) n=7,716 Mean/% (SD)**	**Hospitals with *C. diff* SIR missing (2013-17) n=1,858 Mean/% (SD)**
% 30-Day Hospital Readmissions	15.28 (0.80)	15.23 (0.68)
Length of Stay (days)	3.11 (1.50)	3.25 (2.55)
% 30-Day Mortality	12.86 (1.16)	12.85 (1.13)
ICU[d] Days	1505 (1346)	845 (2567)
Public	20.8%	29.7%
Private For Profit	29.3%	42.5%
Private Not For Profit	49.9%	27.8%
Teaching	15.2%	11.8%
Rural	46.7%	40.5%
Bed Count	92 (78)	54 (110)
Quality Accredited	80.4%	60.4%
Changes in ownership = 0	38.7%	47.1%
Changes in ownership = 1	28.1%	27.3%
Changes in ownership >1	33.2%	25.6%
Compliant with CMS[e] Requirements	78.3%	75.3%
Emergency Services	87.1%	67.8%
% ICU beds	6.17 (6.55)	1.43 (4.02)
ICU Services	64.9%	15.1%
Patient Safety Index	0.89 (0.14)	0.90 (0.10)

[a] Methicillin-resistant *Staphylococcus aureus*
[b] *Clostridioides difficile*
[c] Standardized infection ratio
[d] Intensive Care Unit
[e] Centers for Medicare and Medicaid Services

Appendix Table B.2 Regression-adjusted estimates for the association between MRSA[a] SIR[b] and quality and clinical outcomes after inclusion of CLABSI and CAUTI variables, 2013-2017

	30-Day Hospital Readmissions	Length of Stay	30-Day Mortality	ICU[c] Days
	b(SE)	b(SE)	b(SE)	b(SE)
MRSA SIR	0.011	0.007	0.006	32.488
	(0.011)	(0.005)	(0.010)	(52.013)
CLABSI[d] SIR	-0.015	0.016*	-0.002	52.247
	(0.029)	(0.007)	(0.012)	(78.150)
CAUTI[e] SIR	-0.008	-0.010	-0.002	-175.096*
	(0.014)	(0.005)	(0.014)	(79.117)
Teaching	0.135*	-0.020	0.057	733.218
	(0.066)	(0.030)	(0.051)	(520.306)
Bed Count	-0.000	0.001	-0.000	9.413***
	(0.000)	(0.000)	(0.000)	(1.521)
Quality Accredited	0.159	0.072*	0.061	325.229
	(0.087)	(0.033)	(0.119)	(225.754)
Changes in Ownership = 1	0.076	0.021	-0.061	-475.425
	(0.184)	(0.074)	(0.157)	(312.150)
Changes in Ownership > 1	-0.177	0.046	-0.083	-1.3e+03*
	(0.229)	(0.085)	(0.190)	(508.307)
Compliant with CMS[f] Requirements	0.029	-0.008	-0.008	242.904
	(0.068)	(0.037)	(0.049)	(310.678)
%ICU Beds	0.004	-0.012**	-0.004	529.761***
	(0.004)	(0.004)	(0.004)	(91.855)
Patient Safety Indicator	0.059	-0.037	0.239**	-101.193
	(0.051)	(0.027)	(0.070)	(281.017)
2014	-0.320***	0.028**	-0.320***	207.554**
	(0.042)	(0.009)	(0.014)	(69.251)
2015	0.014	0.031*	1.150***	473.929***
	(0.051)	(0.012)	(0.027)	(134.330)
2016	-0.290***	0.029	0.831***	649.017***
	(0.056)	(0.018)	(0.037)	(125.985)
2017	-0.296***	0.003	0.733***	612.580***
	(0.056)	(0.023)	(0.040)	(146.573)
Constant	15.702***	3.440***	11.886***	325.305
	(0.213)	(0.271)	(0.294)	(1417.925)
N	8414	8258	8029	7850
r2	0.095	0.022	0.630	0.139

[a] Methicillin-resistant *Staphylococcus aureus*
[b] Standardized infection ratio
[c] Intensive Care Unit
[d] Central Line-Associated Blood Stream Infection
[e] Catheter-Associated Urinary Tract Infection
[f] Centers for Medicare and Medicaid Services
* p<0.05 ** p<0.01 *** p<0.001

Appendix Table B.3 Regression-adjusted estimates for the association between *C.diff*[a] SIR[b] and quality and clinical outcomes after inclusion of CLABSI and CAUTI variables, 2013-2017

	30-Day Hospital Readmissions	Length of Stay	30-Day Mortality	ICU[c] Days
	b(SE)	b(SE)	b(SE)	b(SE)
C. diff SIR	0.023	0.025	0.038	39.028
	(0.028)	(0.013)	(0.027)	(125.787)
CLABSI[d] SIR	-0.011	0.016*	-0.001	40.642
	(0.026)	(0.007)	(0.012)	(63.861)
CAUTI[e] SIR	-0.010	-0.008	-0.001	-166.903*
	(0.012)	(0.005)	(0.012)	(73.356)
Teaching	0.118*	-0.006	0.042	648.886
	(0.058)	(0.029)	(0.047)	(465.339)
Bed Count	-0.000	0.001	-0.000	8.990***
	(0.000)	(0.000)	(0.000)	(1.537)
Quality Accredited	0.167	0.070*	0.073	301.393
	(0.085)	(0.033)	(0.110)	(213.688)
Changes in Ownership = 1	0.018	0.014	-0.062	-260.716
	(0.179)	(0.071)	(0.149)	(339.787)
Changes in Ownership > 1	-0.135	0.011	-0.086	-934.166
	(0.221)	(0.081)	(0.182)	(506.852)
Compliant with CMS[f] Requirements	0.023	-0.006	-0.006	251.783
	(0.065)	(0.036)	(0.048)	(299.644)
%ICU Beds	0.004	-0.011**	-0.004	472.986***
	(0.003)	(0.004)	(0.005)	(88.109)
Patient Safety Indicator	0.055	-0.039	0.228**	-117.538
	(0.049)	(0.027)	(0.065)	(269.471)
2014	-0.326***	0.027**	-0.322***	198.390**
	(0.041)	(0.010)	(0.013)	(64.583)
2015	0.010	0.027*	1.146***	473.178***
	(0.050)	(0.013)	(0.026)	(133.280)
2016	-0.290***	0.024	0.829***	634.874***
	(0.053)	(0.018)	(0.036)	(120.649)
2017	-0.290***	0.001	0.741***	600.368***
	(0.052)	(0.023)	(0.037)	(132.871)
Constant	15.677***	3.402***	11.873***	626.891
	(0.203)	(0.259)	(0.292)	(1364.925)
N	9761	9576	9096	9086
r2	0.093	0.021	0.627	0.127

[a] *Clostridioides difficile*
[b] Standardized infection ratios
[c] Intensive Care Unit
[d] Central Line-Associated Blood Stream Infection
[e] Catheter-Associated Urinary Tract Infection
[f] Centers for Medicare and Medicaid Services
* p<0.05 ** p<0.01 *** p<0.001

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